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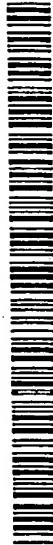
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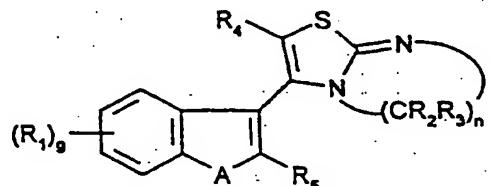
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(54) Title: THIAZOLODERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

WO 00/71549 A1



(1)

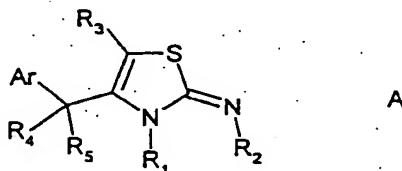
(57) Abstract: Compounds of formula (I); processes to prepare such compounds; compositions containing such compounds and their use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, and their use in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage and as an aid to smoking cessation; are described.

treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage and as an aid to smoking cessation; are described.

## THIAZOLODERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to certain novel substituted dihydroimidazo[2,1-*b*]thiazole and dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine compounds which have affinity for 5-HT<sub>1A</sub> receptors and which inhibit neuronal reuptake of 5-hydroxytryptamine and/or noradrenaline, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, as an aid to smoking cessation and in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage.

WO 98/41528 discloses that compounds of formula A



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including pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which:

Ar is phenyl, naphthyl or benzo[*b*]thiophenyl, each of which may be optionally substituted by one or more substituents selected from a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) a phenoxy group optionally substituted by one or more halo or f) phenyl optionally substituted by one or more halo;

R<sub>1</sub> and R<sub>2</sub>, which may be the same or different, independently are a) H, b) an alkyl group containing 1 to 6 carbon atoms, c) an alkenyl group containing 3 to 6 carbon

atoms, d) a cycloalkyl group containing 3 to 7 carbon atoms, e) a cycloalkylmethyl group in which the ring contains 3 to 7 carbon atoms, f) an aryl or heteroaryl group optionally substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii)

5 an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, g) an arylalkyl or heteroarylalkyl group in which the alkyl chain contains 1 to 3 carbon atoms and in which the aryl or heteroaryl group may optionally be substituted by one or more substituents selected from i) halo, ii) an

10 alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo; or R<sub>1</sub> and R<sub>2</sub> form an alkylene chain optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms, such

15 that, together with the atoms to which they are attached, they form a 5 or 6 membered ring,

R<sub>3</sub> is a) H, b) an aryl or heteroaryl group optionally substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3

20 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an arylmethyl group in which the aryl is optionally substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3

25 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo; or d) an alkoxyalkyl group containing 3 to 6 carbon atoms; and

R<sub>4</sub> and R<sub>5</sub>, which may be the same or different, independently are an alkyl group containing 1 to 3 carbon atoms, or R<sub>4</sub> and R<sub>5</sub> together with the atom to which they

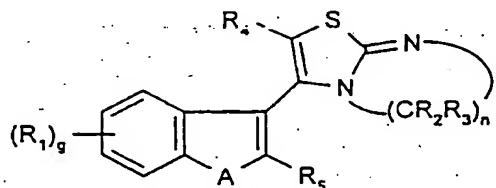
30 are attached form a cycloalkyl ring containing 3 to 6 carbon atoms;

are useful in the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, and as neuroprotective agents to protect against conditions such as stroke. The compounds of the present invention are not disclosed or suggested in this document.

Sharpe C.J and Shadbolt R.S. (Journal of Medicinal Chemistry, 1971, Vol 14 No.10, p977-982) disclose certain dihydroimidazo[2,1-*b*]thiazole compounds having antidepressant activity. However, the document also states that these compounds were generally less active and more toxic than the imidazolines also disclosed in the document. The compounds of the present invention are not disclosed or suggested in this document.

WO 97/02269 discloses that compounds of formula B

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B

including pharmaceutically acceptable salts thereof  
in which

A is S(O)<sub>p</sub> or O;

15. p is 0, 1 or 2;

g is 0, 1, 2, 3, or 4;

n is 2 or 3;

R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) a hydroxalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxy carbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being 20 the same or different when g is 2, 3 or 4;

R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> independently are H or an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; and

R<sub>5</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) a hydroxalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxy carbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphonamoyl or sulphonamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, or n) H;

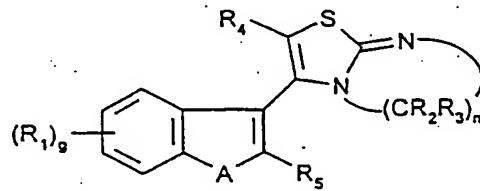
have affinity for 5-HT<sub>1A</sub> receptors and inhibit neuronal reuptake of 5-hydroxytryptamine and/or noradrenaline. These compounds are stated to be useful in the treatment of CNS disorders. However, these compounds exhibit activity as monoamine oxidase inhibitors and/or have affinity for other receptors, for example muscarinic receptors, and are therefore likely to cause undesired side effects. Surprisingly the present invention provides compounds with unexpectedly superior selectivity and efficacy. The compounds of the present invention are not disclosed or suggested in WO 97/02269.

25

US4,160,768 discloses that 3-(2-benzofuranyl)-5,6-dihydroimidazo[2,1-b]thiazole is useful as an anti-inflammatory agent. This document does not disclose or suggest the compounds of the present invention.

30

The present invention provides compounds of Formula I



including pharmaceutically acceptable salts thereof in which

A is S or O;

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g is 0, 1, 2, 3 or 4;

n is 2 or 3;

10 R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g)

15 a hydroxyalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alcoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two

20 alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being the same or different when g is 2, 3 or 4;

R<sub>2</sub> and R<sub>3</sub> are each H;

25

R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, an  $\alpha$ -hydroxy(2-C<sub>1-3</sub>alkoxyphenyl)methyl group, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, a hydroxycycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 8 carbon atoms, an arylalkenyl group containing 8 to 10 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a C<sub>3-7</sub>alkynylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>4-7</sub>cycloalkylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkylthioC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group,

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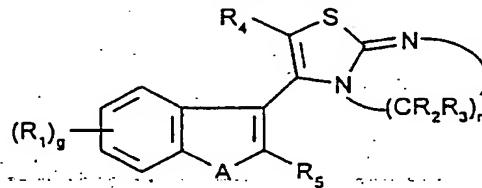
35 a C<sub>1-3</sub>alkylthio group, an arylthio group, a C<sub>1-6</sub> alkanoyl group, a C<sub>3-6</sub>

alkoxycarbonylalkyl group, cyano, halo, a C<sub>1-4</sub>alkyliminomethyl group, a C<sub>1-4</sub>alkylaminoalkyl group or a hydroxyiminomethyl group;

R<sub>5</sub> is H or halo.

5

In a preferred aspect the present invention provides compounds of Formula I



including pharmaceutically acceptable salts thereof in which

10 A is S or O;

g is 0, 1, 2, 3, or 4;

n is 2 or 3;

15

R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphanyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) a hydroxalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being the same or different when g is 2, 3 or 4;

20

25 R<sub>2</sub> and R<sub>3</sub> are each H;

30 R<sub>2</sub> and R<sub>3</sub> are each H;

R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, a 5 hydroxycycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 8 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkylthioC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group, a C<sub>1-3</sub>alkylthio group, a C<sub>1-6</sub> alkanoyl group, halo, a C<sub>1-4</sub>alkyliminomethyl group or a hydroxyiminomethyl group ; and

10

R<sub>5</sub> is H or halo.

It will be understood that the term halo, when used herein, includes fluoro, chloro, bromo and iodo. It will be understood that in alkyl groups, alkenyl groups, 15 alkynyl groups, alkylthio groups and alkoxy groups containing more than two carbon atoms the alkyl group may be straight or branched. Aryl is used to indicate phenyl optionally substituted by one or more of the following: a C<sub>1-3</sub>alkyl group, a C<sub>1-3</sub> alkoxy group or halo.

20

In a first group of preferred compounds of the present invention A is S.

In a second group of preferred compounds of the present invention A is O.

Preferably g is 0 or 1 and R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 25 carbon atoms optionally substituted by one or more halo, or c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo. Preferably R<sub>1</sub> is in the 5-position of the benzo[b]thiophene ring. More preferably g is 0 or 1 and R<sub>1</sub> is halo or an alkoxy group containing 1 to 3 carbon atoms. Most preferably g is 0 or 1 and R<sub>1</sub> is chloro or methoxy.

30

Preferably n is 2.

Preferably R<sub>2</sub> and R<sub>3</sub> are each H.

35

Preferably R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is

## 8.

not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, an alkenyl group containing 2 carbon atoms optionally substituted by one or more C<sub>1-2</sub>alkyl groups , a C<sub>1-4</sub> alkyliminomethyl group or a hydroxyiminomethyl group. More preferably R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 5 carbon atoms, a hydroxyalkenyl group containing 3 to 5 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond or an alkenyl group containing 2 carbon atoms optionally substituted by one or more methyl groups. Most preferably R<sub>4</sub> represents hydroxymethyl or vinyl. Hydroxymethyl is especially preferred for R<sub>4</sub>.

Preferred values of R<sub>4</sub> are hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl; 1-hydroxypropyl, 1-hydroxy-2-methylpropyl, 1-hydroxybutyl, 1-hydroxy-3-methylbutyl, 1-hydroxypentyl, 1-hydroxypropenyl, 1-hydroxybut-3-enyl, 1-hydroxy-2-methylpropenyl, 1-hydroxy-2-methylbut-3-enyl, 1-hydroxypent-4-enyl, 1-hydroxypropynyl, 1-hydroxybut-2-ynyl, methoxymethyl, ethoxymethyl, methylthio, bromo, chloro, vinyl, allyl, 1-methylvinyl, formyl, acetyl, N-(1-methylethyl)iminomethyl, and hydroxyiminomethyl. More preferably R<sub>4</sub> is hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl; 1-hydroxypropyl, 1-hydroxy-2-methylpropyl, 1-hydroxybutyl, 1-hydroxy-3-methylbutyl, 1-hydroxypentyl, 1-hydroxypropenyl, 1-hydroxybut-3-enyl, 1-hydroxy-2-methylpropenyl, 1-hydroxy-2-methylbut-3-enyl, 1-hydroxypent-4-enyl, 1-hydroxypropynyl, 1-hydroxybut-2-ynyl, vinyl, 1-methylvinyl, acetyl, N-(1-methylethyl)iminomethyl, and hydroxyiminomethyl. Most preferably R<sub>4</sub> is hydroxymethyl or vinyl. Hydroxymethyl is especially preferred.

Preferably R<sub>5</sub> is H.

Preferably n is 2.

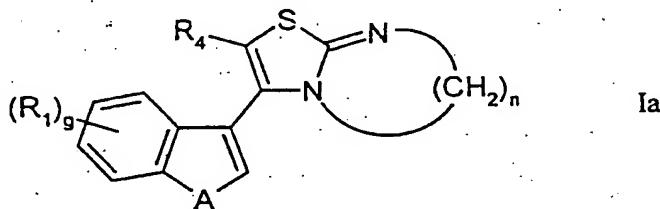
In a preferred group of compounds of Formula I, A is S, g is 0 or 1; n is 2; R<sub>1</sub> is halo or an alkoxy group containing 1 to 3 carbon atoms; R<sub>2</sub> and R<sub>3</sub> are each H; R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 5 carbon atoms, a hydroxyalkenyl group containing 3 to 5 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond or

an alkenyl group containing 2 carbon atoms optionally substituted by one or more methyl groups; and R<sub>5</sub> is H.

In a preferred group of compounds of Formula I, preferably g is 0 or 1 and R<sub>1</sub> is chloro or methoxy. More preferably R<sub>1</sub> is in the 5-position of the benzo[b]thiophene ring.

In a further preferred aspect the present invention provides compounds of Formula Ia

10



including pharmaceutically acceptable salts thereof in which

A is S or O;

15

g is 0, 1, 2, 3 or 4;

n is 2 or 3;

20 R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g)

25 a hydroxyalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two

30 alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being the same or different when g is 2, 3 or 4; and

R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, an  $\alpha$ -hydroxy(2-C<sub>1-3</sub> alkoxyphenyl)methyl group, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a 5 hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, an alkenyl group containing 2 to 8 carbon atoms, an arylalkenyl group containing 8 to 10 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a C<sub>3-7</sub>alkynylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>4-7</sub>cycloalkylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkylthioC<sub>1-3</sub>alkyl 10 group, a C<sub>1-3</sub>alkoxy group, a C<sub>1-3</sub>alkylthio group, an arylthio group, a C<sub>1-6</sub>alkanoyl group, a C<sub>3-6</sub> alkoxy carbonylalkyl group, cyano, halo, a C<sub>1-4</sub>alkyliminomethyl group, a C<sub>1-4</sub>alkylaminomethyl group or a hydroxyiminomethyl group.

In a first group of preferred compounds of the present invention A is S. 15 Preferably n is 2 in this group of compounds. Preferably g is 0 or 1 in this group of compounds. Preferably R<sub>1</sub> is halo, an alkoxy group containing 1 to 3 carbon atoms, or an alkylthio group containing 1 to 3 carbon atoms.

In a second group of preferred compounds of the present invention A is O. 20 Preferably n is 2 in this group of compounds. Preferably g is 0 or 1 in this group of compounds. Preferably R<sub>1</sub> is halo, an alkoxy group containing 1 to 3 carbon atoms, or an alkylthio group containing 1 to 3 carbon atoms.

In compounds of Formula I and Formula Ia preferred values of R<sub>1</sub> are methyl, 25 ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, isopropoxy, bromo, chloro, fluoro, iodo, trifluoromethyl, trifluoromethoxy, methylthio, methylsulphinyl, methylsulphonyl, hydroxy, formyloxy, acetoxy, hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, 1-hydroxypropyl, cyano, formyl, acetyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, carbamoylmethyl, sulphamoyl, sulphamoylmethyl, 30 amino, methylamino, dimethylamino, ethylamino or diethylamino. More preferably R<sub>1</sub> is methoxy, chloro or methylthio.

In compounds of Formula I and Formula Ia preferred values of R<sub>4</sub> are cyclopropyl, methoxy, ethoxy, bromo, chloro, fluoro, iodo, trifluoromethyl, 35 trifluoromethoxy, hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl; 1-

hydroxypropyl, 1-hydroxy-2-methylpropyl, 1-hydroxybutyl, 1-hydroxy-3-methylbutyl,  
1-hydroxypentyl, 1-hydroxypropenyl, 1-hydroxybut-3-enyl, 1-hydroxy-2-  
methylpropenyl, 1-hydroxy-2-methylbut-3-enyl, 1-hydroxypent-4-enyl, 3-hydroxybut-  
1-enyl, 1-hydroxypropynyl, 1-hydroxybut-2-ynyl,  $\alpha$ -hydroxy-2-methoxybenzyl,  
5 methoxymethyl, ethoxymethyl, isopropoxymethyl, cyclopropylmethoxymethyl,  
cyclobutylmethoxymethyl, prop-2-nyloxyethyl, methylthio, phenylthio, vinyl, allyl,  
prop-1-enyl, 2-methylprop-2-enyl, 1-methylvinyl, styryl, formyl, acetyl, cyano,  
ethoxycarbonylmethyl, *N*-(1-methylethyl)iminomethyl, *N*-methylaminomethyl and  
hydroxyiminomethyl. More preferably  $R_4$  is hydroxymethyl, 1-hydroxyethyl or vinyl.

10 Most preferably  $R_4$  is hydroxymethyl or vinyl.

In especially preferred compounds of Formula Ia, A is S or O; g is 0 or 1, n is 2;  $R_1$  represents halo, an alkoxy group containing 1 to 3 carbon atoms or an alkylthio group containing 1 to 3 carbon atoms; and  $R_4$  represents a hydroxyalkyl group containing 1 to 4 carbon atoms, an  $\alpha$ -hydroxy(2-C<sub>1-3</sub>alkoxyphenyl)methyl group, a hydroxyalkenyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, an alkenyl group containing 2 to 3 carbon atoms, a 15 C<sub>1-3</sub>alkylthio group, a C<sub>1-2</sub> alkanoyl group or a hydroxyiminomethyl group.  
20

In the remainder of this description the term "compounds of Formula I" means compounds of Formula I or compounds of Formula Ia. Similarly the term "a compound of Formula I" means a compound of Formula I or a compound of Formula 25 Ia.

Compounds of Formula I may exist as salts with pharmaceutically acceptable acids. The present invention includes all such salts. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, 30 formates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, oxalates, benzoates and salts with amino acids such as glutamic acid. Such salts are prepared by methods known to those skilled in the art as illustrated in the Examples.

Certain compounds of Formula I may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of Formula I and mixtures thereof.

5        Certain compounds of Formula I may exist in different stable conformational forms which may be separable. For example, if a bulky group is present there may be restricted rotation about one or more single bond or bonds due to steric hindrance. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit.  
10      separation of different conformers. The present invention includes each conformational isomer of compounds of Formula I and mixtures thereof.

Certain compounds of Formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Certain compounds of Formula I contain one or more chiral centres, and exist  
20      in different optically active forms. When compounds of Formula I contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallisation;  
25      formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of Formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of Formula I and mixtures thereof.

Specific compounds of Formula I are:-

10 3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde;  
[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;

15 3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde oxime;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]ethanol;

20 3-(benzo[b]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole;  
3-(benzo[b]thiophen-3-yl)-2-bromo-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine;

25 1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-methylethanol;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]propan-1-ol;

30 2-bromo-3-(5-methoxybenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
2-bromo-3-(5-chlorobenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

35 3-(benzo[b]thiophen-3-yl)-2-ethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-en-1-ol;

40 3-(benzo[b]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole;  
2-allyl-3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

45 [3-(benzo[b]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;  
*N*-(3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl)methylidene)-1-methylethylamine;

50 3-(benzo[b]thiophen-3-yl)-2-chloro-5,6-dihydroimidazo[2,1-*b*]thiazole;  
2-acetyl-3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
3-(benzo[b]thiophen-3-yl)-2-(methoxymethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(benzo[*b*]thiophen-3-yl)-2-(methylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(benzo[*b*]thiophen-3-yl)-2-(1-methylvinyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

5 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylpropan-1-ol ;

10 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]butan-1-ol ;

15 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylbut-3-en-1-ol ;

20 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-3-methylbutan-1-ol;

25 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pentan-1-ol;

30 [1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl](2-methoxyphenyl)methanol;

35 3-(benzo[*b*]thiophen-3-yl)-2-prop-1-enyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

40 [3-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-2-yl]methanol;

45 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carbonitrile;

50 3-(benzo[*b*]thiophen-3-yl)-2-styryl-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde;

[3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;

3-(benzo[*b*]thiophen-3-yl)-2-(phenylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole;

4-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-en-2-ol;

3-(benzo[*b*]thiophen-3-yl)-2-(2-methylprop-2-enyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

ethyl [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]acetate;  
2-bromo-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole;  
5 {3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazol-2-  
ylyl}methanol;  
10 3-(benzo[*b*]thiophen-3-yl)-2-cyclopropylmethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;  
3-(benzo[*b*]thiophen-3-yl)-2-prop-2-ynyloxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;  
15 2-bromo-3-(7-methoxybenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
3-(benzo[*b*]thiophen-3-yl)-2-isopropoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole; and  
20 3-(benzo[*b*]thiophen-3-yl)-2-cyclobutylmethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole  
including pharmaceutically acceptable salts thereof and individual enantiomers,  
racemates or other mixtures of enantiomers.

The present invention also includes pharmaceutical compositions comprising  
25 a therapeutically effective amount of a compound of Formula I or a salt thereof  
together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a compound of  
Formula I or a salt thereof. In therapeutic use, the active compound may be  
30 administered orally, rectally, parenterally or topically, preferably orally. Thus the  
therapeutic compositions of the present invention may take the form of any of the  
known pharmaceutical compositions for oral, rectal, parenteral or topical  
administration. Pharmaceutically acceptable carriers suitable for use in such  
compositions are well known in the art of pharmacy. The compositions of the  
35 invention may contain 0.1-99% by weight of active compound. The compositions of  
the invention are generally prepared in unit dosage form. Preferably the unit dosage  
of active ingredient is 1-500 mg. The excipients used in the preparation of these  
compositions are the excipients known in the pharmacist's art.

40 Compositions for oral administration are the preferred compositions of the  
invention and these are the known pharmaceutical forms for such administration, for  
example tablets, capsules, syrups and aqueous or oil suspensions. The excipients

used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and 5 tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active 10 compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the 15 presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Preferably the compositions of the invention are administered orally in the 20 known pharmaceutical forms for such administration. Dosage forms suitable for oral administration may comprise tablets, pills, capsules, caplets, multiparticulates including: granules, beads, pellets and micro-encapsulated particles; powders, elixirs, syrups, suspensions and solutions.

25 Solid oral dosage forms, for example tablets, may be prepared by mixing the pharmaceutical composition of the present invention with one or more of the following ingredients or mixtures thereof:  
inert diluents, for example calcium carbonate, calcium sulphate, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, glyceryl palmitostearate, hydrogenated vegetable oil, kaolin, lactose, 30 magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinized starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc and tribasic calcium phosphate;  
35 disintegrating agents, for example alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium,

crospovidone, guar gum, magnesium aluminium silicate, methylcellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate, starch including maize starch and agar;

5 lubricating agents, for example calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid, talc and zinc stearate;

binders, for example acacia, alginic acid, carbomer, carboxymethylcellulose sodium,

10 dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, liquid glucose, magnesium aluminium silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch including maize starch, zein, sugars (such as sucrose, molasses and lactose), and natural and synthetic gums

15 (such as extract of Irish moss, polyethylene glycol, waxes, microcrystalline cellulose and polyvinylpyrrolidone);

colouring agents, for example conventional pharmaceutically acceptable dyes;

sweetening and flavouring agents;

preservatives;

20 one or more pharmaceutically acceptable couple or couples (such as those comprising an acid and a carbonate or bicarbonate salt), which effervesces to aid dissolution when the solid dosage form is added to water; and

other optional ingredients known in the art to permit production of oral dosage forms by known methods such as tabletting.

25

Solid oral dosage forms may be formulated in a manner known to those skilled in the art so as to give a sustained release of the active compound. Film coated, solid oral dosage forms comprising compositions of the present invention may be advantageous, depending on the nature of the active compound. Various materials, for example shellac and/or sugar, may be present as coatings, or to otherwise modify the physical form of the oral dosage form. For example tablets or pills may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate and/or hydroxy propyl methylcellulose phthalate.

Capsules and/or caplets (for example hard or soft gelatin capsules) comprising the active compound (with or without added excipients such as a fatty oil), may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The contents of the capsule and/or caplet may be 5 formulated using known methods to give sustained release of the active compound.

Liquid oral dosage forms comprising compositions of the present invention may be an elixir, suspension and/or syrup (for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent [such as sodium carboxymethylcellulose] and/or oily suspensions containing the active compound in a suitable vegetable oil [such as arachis oil and/or sunflower oil]). Liquid oral dosage forms may also comprise one or 10 more sweetening agent, flavouring agent, preservatives and/or mixtures thereof.

15 The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to 20 facilitate dispersion in the liquid medium.

25 Preferably each of the above oral dosage forms may contain from about 1 mg to about 1000 mg, more preferably from about 5 mg to about 500 mg (for example 10 mg, 50 mg, 100 mg, 200 mg, or 400 mg) of the active compound.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with hard fat, semi-synthetic glyceride, cocoa butter and/or polyethylene glycol bases.

30 Pharmaceutical compositions may also be administered parenterally (for example subcutaneously, intramuscularly, intradermally and/or intravenously [such as by injection and/or infusion] in the known pharmaceutical dosage forms for parenteral administration (for example sterile suspensions in aqueous and/or oily media and/or sterile solutions in suitable solvents, preferably isotonic with the blood 35 of the intended patient). Parenteral dosage forms may be sterilised (for example by micro-filtration and/or using suitable sterilising agents [such as ethylene oxide]).

Optionally one or more of the following pharmaceutically acceptable adjuvants suitable for parenteral administration may be added to parenteral dosage forms: local anaesthetics, preservatives, buffering agents and/or mixtures thereof. Parenteral dosage forms may be stored in suitable sterile sealed containers (for example ampoules and/or vials) until use. To enhance stability during storage the parenteral dosage form may be frozen after filling the container and fluid (for example water) may be removed under reduced pressure.

Pharmaceutical compositions may be administered nasally in known pharmaceutical forms for such administration (for example sprays, aerosols, nebulised solutions and/or powders). Metered dose systems known to those skilled in the art (for example aerosols and/or inhalers) may be used.

Pharmaceutical compositions may be administered to the buccal cavity (for example sub-lingually) in known pharmaceutical forms for such administration (for example slow dissolving tablets, chewing gums, troches, lozenges, pastilles, gels, pastes, mouthwashes, rinses and/or powders).

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid

such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

10

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

15

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The present invention also comprises a compound of Formula I for use as a medicament.

20

The pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula I may be used to treat depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress in mammals particularly humans, and as an aid to smoking cessation in human beings. In addition such compositions may be used in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to

1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

In yet another aspect, the present invention provides the use of a compound 5 of Formula I in the manufacture of a medicament for use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent 10 diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, as an aid to smoking cessation and in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage.

15 The present invention also provides a method of treating depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, 20 hyperlipidaemia, stress and seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

25 The present invention also provides a method of reducing the craving to smoke in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof. The present invention also provides a method of reducing weight gain after smoking 30 cessation in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

In addition the compounds of the present invention may be useful in the treatment or prevention of metabolic diseases and conditions arising therefrom, for 35 example non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence,

hyperactivity disorders, hiatal hernia and reflux esophagitis, pain, especially neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

5

The compounds of the present invention may be useful in preventing cardiovascular disease, and in reducing platelet adhesiveness, in aiding weight loss after pregnancy and in aiding weight loss after smoking cessation.

10

The compounds of the present invention are particularly useful in treating obesity and related co-morbid conditions, for example, diabetes, hyperglycaemia and hyperlipidaemia. It is known that monoamine reuptake inhibitors which are used to treat obesity are often associated with cardiovascular side effects, for example, increased heart rate and increased blood pressure. The compounds of the present invention reduce the cardiovascular side effects which might be expected to occur from the administration of a monoamine reuptake inhibitor particularly a noradrenaline reuptake inhibitor. Whilst not wishing to be bound by theory it is likely that the combination of 5-HT<sub>1A</sub> agonism in the compounds of the present invention reduces the cardiovascular side effects which might have arisen from their monoamine reuptake inhibition particularly their noradrenaline reuptake inhibition.

15

20

In another aspect the present invention provides a method of reducing the cardiovascular side effects of an anti-obesity drug comprising incorporating into the compound 5-HT<sub>1A</sub> agonism.

25

In another aspect the present invention provides the use of a compound which is a 5-HT<sub>1A</sub> agonist and which is a monoamine reuptake inhibitor particularly a noradrenaline reuptake inhibitor in the treatment of obesity and related co-morbid conditions without causing cardiovascular side effects.

30

35

The beneficial properties of especially preferred compounds of the present invention in reducing cardiovascular side-effects may be demonstrated in rat telemetry studies in which heart rate, blood pressure, body temperature and locomotor activity are recorded continuously over time. Suitable methods are described in:

Brockway, BP, Mills, PA & Azar, SH (1991) A new method for continuous chronic measurement of blood pressure, heart rate and activity in the rat via radio-telemetry. Clinical and Experimental Hypertension - Theory and Practice A13(5), 885-895 and Guiol, C, Ledoussal, C & Surgé, J-M (1992) A radiotelemetry system for chronic measurement of blood pressure and heart rate in the unrestrained rat. Validation of method. Journal of Pharmacological and Toxicological Methods 28, 99-105.

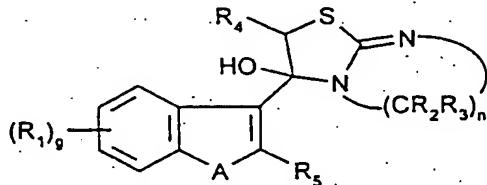
The 5-HT<sub>1A</sub> agonism of especially preferred compounds of the present invention may be determined by electrophysiology by methods known to those skilled in the art.

Processes for the preparation of compounds of Formula I will now be described. The processes may be performed on an individual basis, or by multiple parallel synthesis, also known as High Speed Analoguing. The processes are preferably carried out at atmospheric pressure.

Compounds of Formula I may be prepared by methods disclosed in WO 97/02269. Additionally compounds of Formula I may be prepared by methods described below.

20

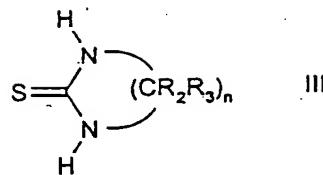
Compounds of Formula I may be prepared by dehydrating a compound of Formula II



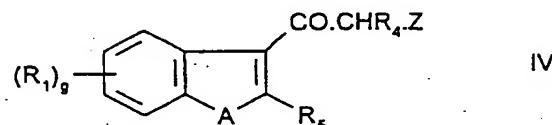
II

25 in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, g and n are as hereinbefore defined, optionally in the presence of an acid, for example acetic or sulphuric acid, at a temperature in the range 0-200°C; preferably in the range 20-150°C.

Compounds of Formula II may be prepared by reacting a compound of  
30 Formula III



in which R<sub>2</sub>, R<sub>3</sub> and n are as hereinbefore defined, with a compound of Formula IV

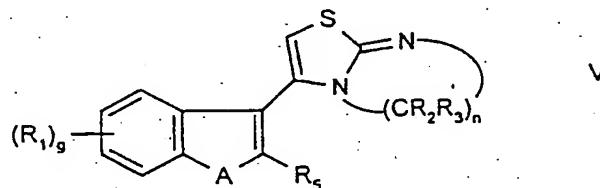


5

in which Z is a leaving group, for example a halo such as bromo, and A, R<sub>1</sub>, R<sub>4</sub>, R<sub>5</sub> and g are as hereinbefore defined, at a temperature in the range 0-200°C, in the presence of a solvent, for example ethanol and optionally in the presence of an acid, for example acetic acid; preferably by heating at a temperature in the range 20°C to 10 the boiling point of the solvent used.

Compounds of Formula I may also be prepared directly by reacting a compound of Formula III with a compound of Formula IV at a temperature in the range of 0-200°C, optionally in the presence of an acid, for example acetic acid, and 15 optionally in the presence of a solvent, for example ethanol, without isolation of the intermediate of Formula II; preferably by heating at a temperature in the range 20-150°C.

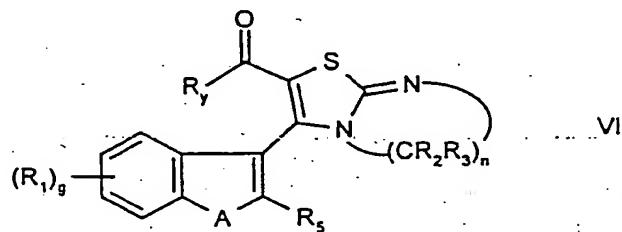
Compounds of Formula I in which R<sub>4</sub> represents halo may be prepared by 20 reacting a compound of Formula V



25 in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined, with a halogenating agent for example bromine, phenyltrimethylammonium tribromide, iodine monochloride or benzyltrimethylammonium tetrachloroiodate at a temperature in the

range -50-200°C optionally in the presence of a solvent, for example dichloromethane, tetrahydrofuran or acetone.

Compounds of Formula I in which R<sub>4</sub> represents a group of Formula  
 5 -CH(OH)R<sub>x</sub> in which R<sub>x</sub> is a C<sub>1-5</sub> alkyl group, an alkenyl group containing 2-5 carbon atoms, an alkynyl group containing 2-5 carbon atoms or (2-C<sub>1-3</sub>alkoxyphenyl) may be prepared by reacting a compound of Formula VI



10 in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined and R<sub>y</sub> is H with an organometallic reagent, for example a compound of formula R<sub>x</sub>MgX or R<sub>x</sub>Li in which R<sub>x</sub> is as hereinbefore defined and X is halo, for example bromo, in the presence of a solvent, for example tetrahydrofuran or ether, at a temperature in the range of -50°C to the boiling point of the solvent used.

15

Compounds of Formula I in which R<sub>4</sub> represents a group of Formula -CH(OH)R<sub>y</sub> in which R<sub>y</sub> is a C<sub>1-5</sub> alkyl group, an alkenyl group containing 2-5 carbon atoms, an alkynyl group containing 2-5 carbon atoms or (2-C<sub>1-3</sub>alkoxyphenyl) may be prepared by reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> is a C<sub>1-5</sub> alkyl group, an alkenyl group containing 2-5 carbon atoms, an alkynyl group containing 2-5 carbon atoms or (2-C<sub>1-3</sub>alkoxyphenyl) with a reducing agent, for example sodium borohydride, in the presence of a solvent, for example ethanol, at a temperature in the range of 0°C to the boiling point of the solvent used.

25

Compounds of Formula I in which R<sub>4</sub> is hydroxymethyl may be prepared by reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> is H with a reducing agent, for example sodium borohydride, in a solvent, for example methanol, at a temperature in the range of -50°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> is hydroxyiminomethyl may be prepared by reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> is H with hydroxylamine or a salt thereof optionally in the presence of a solvent, for example an alcohol, eg ethanol, at a temperature in the range of 0-250°C.

Compounds of Formula I in which R<sub>4</sub> is cyano may be prepared by reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined and R<sub>y</sub> is H with hydroxylamine or a salt thereof in the presence of formic acid at a temperature in the range of 0-250°C.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkyliminomethylene group may be prepared by reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined and R<sub>y</sub> represents H with an amine of formula R<sub>a</sub>NH<sub>2</sub> wherein R<sub>a</sub> represents a C<sub>1-4</sub> alkyl group optionally in the presence of a solvent, for example ethanol, optionally in the presence of an acid catalyst, for example acetic acid, at a temperature in the range 0-250°C.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkylaminomethylene group may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkyliminomethylene group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined, with a reducing agent, for example sodium borohydride, in the presence of a solvent, for example an alcohol e.g. ethanol, at a temperature in the range 0°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkylaminomethylene group may be prepared directly from a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined and R<sub>y</sub> represents hydrogen by reaction with an amine of formula R<sub>a</sub>NH<sub>2</sub> wherein R<sub>a</sub> represents a C<sub>1-4</sub> alkyl group and a reducing agent, for example sodium triacetoxyborohydride, in the presence of a solvent, for example tetrahydrofuran, at a temperature in the range 0°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> represents a group of formula -C(OH)R<sub>x</sub>R<sub>y</sub> in which R<sub>x</sub> and R<sub>y</sub> are each independently a C<sub>1-5</sub> alkyl group may be

prepared by reacting a compound of Formula VI in which R<sub>y</sub> is a C<sub>1-5</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with an organometallic reagent, for example a compound of formula R<sub>x</sub>MgX or R<sub>x</sub>Li in which R<sub>x</sub> is as hereinbefore defined and X is halo, for example bromo, in the presence of a solvent, for example tetrahydrofuran or ether, at a temperature in the range of -50°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> represents a group of formula -C(OH)R<sub>x</sub>R<sub>y</sub> in which R<sub>x</sub> and R<sub>y</sub> are the same C<sub>1-2</sub> alkyl group may be prepared by reacting a compound of Formula VI, as hereinbefore defined except that R<sub>y</sub> is OR<sub>z</sub> in which R<sub>z</sub> is a C<sub>1-6</sub>alkyl group, with an organometallic reagent, for example a compound of formula R<sub>x</sub>MgX or R<sub>x</sub>Li in which R<sub>x</sub> is as hereinbefore defined and X is halo, for example bromo, in the presence of a solvent, for example tetrahydrofuran or ether, at a temperature in the range of -50°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>2-6</sub> alkenyl group in which the double bond is attached to the carbon alpha to the thiazole ring or a styryl group may be prepared by reacting compounds of Formula VI, in which R<sub>y</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a phosphonium salt of formula R<sub>z</sub>Ph<sub>3</sub>P<sup>+</sup>Br<sup>-</sup> in which R<sub>z</sub> represents a C<sub>1-5</sub> alkyl group or a benzyl group in the presence of a base for example n-butyllithium, in a solvent for example, an ether, e.g. tetrahydrofuran, at a temperature in the range -78°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>2-6</sub> alkanoyl group may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents halo, for example bromo or chloro, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, or a compound of Formula V with a compound of formula R<sub>b</sub>MgX or R<sub>b</sub>Li in which R<sub>b</sub> is a C<sub>1-6</sub> alkyl group and X is halo, for example bromo or chloro, in the presence of a solvent for example an ether, eg diethyl ether or tetrahydrofuran, at a temperature in the range -78°C to the boiling point of the solvent used, and then reacting the product obtained with an acylating agent for example a compound of Formula R<sub>c</sub>CON(CH<sub>3</sub>)OCH<sub>3</sub> in which R<sub>c</sub> represents a C<sub>1-5</sub> alkyl group in a solvent, for example an ether e.g. tetrahydrofuran, at a temperature in the range 0°C to the

boiling point of the solvent used. Compounds of Formula VI may be prepared in a similar manner.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkoxyC<sub>1-3</sub> alkyl group 5 may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents a hydroxyC<sub>1-3</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a C<sub>1-3</sub> alkylating agent, for example a C<sub>1-3</sub> alkyl halide e.g. a C<sub>1-3</sub> alkyl iodide in the presence of a base, for example sodium hydride, in a solvent, for example N,N-dimethylformamide, at a temperature in the range of -50 to 150°C.

10

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>4-7</sub>cycloalkylalkoxyC<sub>1-3</sub>alkyl group may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents a hydroxyC<sub>1-3</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a C<sub>4-7</sub>cycloalkylalkylating agent, for example a 15 C<sub>4-7</sub>cycloalkylalkyl halide e.g. a C<sub>4-7</sub>cycloalkylalkyl iodide in the presence of a base, for example sodium hydride, in a solvent, for example N,N-dimethylformamide, at a temperature in the range of -50 to 150°C.

20

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>3-7</sub>alkynylalkoxyC<sub>1-3</sub>alkyl group may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents a hydroxyC<sub>1-3</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a C<sub>3-7</sub>alkynylalkylating agent, for example a C<sub>3-7</sub>alkynylalkyl halide e.g. a C<sub>3-7</sub>alkynylalkyl iodide in the presence of a base, for example sodium hydride, in a solvent, for example N,N-dimethylformamide, at a temperature in the range of -50 to 25 150°C.

30

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkylthioC<sub>1-3</sub> alkyl group may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents a mercaptoC<sub>1-3</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a C<sub>1-3</sub> alkylating agent, for example a C<sub>1-3</sub> alkyl halide e.g. a C<sub>1-3</sub> alkyl iodide in the presence of a base, for example sodium hydride or sodium hydroxide, in a solvent, for example N,N-dimethylformamide, at a temperature in the range of -50 to 150°C.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkylthio group or an arylthio group and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents halo or a compound of Formula V with a metallating agent, for example a compound of formula RMgX or RLi in which R is a C<sub>1-6</sub> alkyl group and X is halo, for example chloro, bromo or iodo, in a solvent, for example an ether or a mixture of ethers, eg tetrahydrofuran, or diethyl ether, at a temperature in the range of -100°C to the boiling point of the solvent used to give an intermediate complex, which is reacted with a disulphide of formula R<sub>d</sub>S-SR<sub>d</sub> in which R<sub>d</sub> is a C<sub>1-3</sub> alkyl group or an aryl group, at a temperature in the range of -100°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkoxy group and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents halo, for example bromo or iodo, with an C<sub>1-3</sub> alkoxide salt, for example a sodium or potassium salt, optionally in the presence of a solvent, for example a C<sub>1-3</sub> alcohol or dimethylformamide, optionally in the presence of a catalyst, for example a copper (I) salt, at a temperature in the range of 0-350°C.

20

Compounds of Formula I in which R<sub>4</sub> represents a C<sub>3-6</sub> alkenyl group in which the double-bond is not attached to the carbon alpha to the thiazole ring may be prepared by reacting a compound of Formula I in which R<sub>4</sub> represents halo, for example bromo or chloro, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, or a compound of Formula V with a compound of formula R<sub>b</sub>MgX or R<sub>b</sub>Li in which R<sub>b</sub> is a C<sub>1-6</sub> alkyl group and X is halo, for example bromo or chloro, in the presence of a solvent for example an ether, eg diethyl ether or tetrahydrofuran, at a temperature in the range -78°C to the boiling point of the solvent used, and then reacting the product obtained with an alkenylating agent, for example a C<sub>3-6</sub>alkenylmethyl halide e.g. a C<sub>3-6</sub>alkenylmethyl iodide, in a solvent, for example an ether e.g. tetrahydrofuran, at a temperature in the range 0°C to the boiling point of the solvent used.

Compounds of Formula I in which R<sub>4</sub> is a C<sub>3-6</sub>alkoxycarbonylalkyl group may be prepared by reacting compounds of Formula VI, in which R<sub>y</sub> represents hydrogen and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a phosphonate of formula Me<sub>2</sub>NCH[PO(OR<sub>2</sub>)<sub>2</sub>]<sub>2</sub> in which R<sub>2</sub> represents a C<sub>1-4</sub> alkyl group in the presence of a base, for example sodium hydride, in a solvent for example an ether, e.g. 1,4-dioxane, at a temperature in the range -78°C to the boiling point of the solvent used, then subjecting the resulting intermediate product to partial hydrolysis in the presence of an acid, for example hydrochloric acid.

10 Compounds of Formula I in which R<sub>4</sub> is a C<sub>4-6</sub>hydroxyalkenyl group in which the double bond is attached to the carbon alpha to the thiazole ring may be prepared by reacting compounds of Formula VI, in which R<sub>y</sub> represents hydrogen and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a compound of Formula (R<sub>2</sub>O)<sub>2</sub>POCH<sub>2</sub>COR<sub>c</sub> in which R<sub>2</sub> represents a C<sub>1-2</sub> alkyl group and R<sub>c</sub> represents a C<sub>1-3</sub> alkyl group in the presence of a base, for example sodium hydride, in a solvent for example an ether, e.g. tetrahydrofuran, at a temperature in the range -78°C to the boiling point of the solvent used, then subjecting the resulting intermediate product to reaction with a reducing agent, for example sodium borohydride, in a solvent, for example ethanol, at a temperature in the range -20°C to the boiling point of the solvent used.

25 Compounds of Formula III are commercially available or may be prepared by methods known to those skilled in the art. Compounds of Formula IV may be prepared by methods known to those skilled in the art as specified in the individual Examples described herein.

The ability of compounds of Formula I to interact with 5-hydroxytryptamine (5-HT) receptors has been demonstrated for the products of Examples 1 to 56 by the following test which determines the ability of the compounds to inhibit tritiated ligand 30 binding to 5-HT receptors *in vitro* and in particular to 5-HT<sub>1A</sub> receptors.

Hippocampal tissue from the brains of male Sprague-Dawley rats (Charles River; weight range 150-250 g) was homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7 when measured at 25°C, 1:40 w/v) and centrifuged at 40,000 g at 4°C for 10 minutes. The pellet was rehomogenised in the same buffer, incubated at 37°C for 10

minutes and centrifuged at 40,000 g at 4°C for 10 minutes. The final pellet was resuspended in 50 mM Tris-HCl buffer (pH 7.7) containing 4 mM CaCl<sub>2</sub>, 0.1% L-ascorbic acid and 10 µM pargyline hydrochloride (equivalent to 6.25 mg wet weight of tissue/ml) and used immediately in the binding assay.

5

Membranes (400 µl; equivalent to 2.5 mg wet weight of tissue/tube) were incubated with 50 µl of [<sup>3</sup>H]8-hydroxy-2-(dipropylamino)tetralin ([<sup>3</sup>H]8-OH-DPAT) at a single concentration of 1 nM and 50 µl of distilled water (total binding) or 50 µl of test compound (at a single concentration of 10<sup>-6</sup> M or at 10 concentrations ranging from 10<sup>-11</sup>-10<sup>-3</sup> M) or 50 µl of 5-HT (10 µM, non-specific binding) at 25°C for 30 minutes. The incubation was terminated by rapid filtration under vacuum through Skatron 11734 filters using a Skatron Cell Harvester. Filters were washed with ice-cold 50 mM Tris-HCl buffer, pH 7.7 (at 25°C, wash setting 9,9,0). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

The ability of compounds of Formula I to interact with 5-hydroxytryptamine (5-HT) reuptake sites has been demonstrated for the products of Examples 1 to 56 by the following test which determines the ability of compounds to displace the standard ligand, [<sup>3</sup>H]citalopram, from 5-HT reuptake sites *in vitro*.

Frontal cortical tissue from the brains of male Charles River rats weighing 150-250 g was homogenised in ice-cold 50 mM Tris-HCl, pH 7.4 (when measured at 25°C) containing 120 mM sodium chloride and 5 mM potassium chloride (Tris buffer; 25 1:30 w/v) and centrifuged at 40,000 g for 10 minutes. The supernatant was discarded and the pellet rehomogenised in Tris buffer, 1:60 w/v, and centrifuged at 40,000 g for 10 minutes. This step was repeated a further time. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.4 containing 120 mM sodium chloride and 5 mM potassium chloride (equivalent to 3.125 mg wet weight of tissue/ml) and used immediately in the binding assay. All centrifugations were performed at 4°C.

Membranes (400 µl; equivalent to 1.25 mg wet weight of tissue/tube) were incubated with 50 µl [<sup>3</sup>H]citalopram at a single concentration of 1.3 nM and 50 µl of distilled water (total binding) or 50 µl of test compound (at a single concentration of 35 10<sup>-6</sup> M or at 10 concentrations ranging from 10<sup>-11</sup>-10<sup>-3</sup> M) or 50 µl of paroxetine

(0.5  $\mu$ M; non-specific binding) for 1 h at 27°C. Membrane bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters presoaked in 0.5% PEI using a Skatron Cell Harvester. Filters were then washed in ice-cold 50 mM Tris-HCl buffer, pH 7.4 (at 25°C, wash setting 9,9,0). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

The ability of compounds of Formula I to interact with noradrenaline (NA) reuptake sites has been demonstrated for the products of Examples 1 to 33 by the following test which determines the ability of compounds to displace the standard ligand, [ $^3$ H]nisoxetine, from noradrenaline reuptake sites *in vitro*.

Frontal cortical tissue from the brains of male Charles River rats weighing 150-250 g was homogenised in ice-cold 50 mM Tris-HCl, pH 7.4 (at 25°C) containing 120 mM sodium chloride and 5 mM potassium chloride (Tris buffer; 1:60 w/v) using a Kinematic polytron (speed setting 6 for 10 seconds) and centrifuged at 40,000 g for 10 minutes. The supernatant was discarded and the pellet rehomogenised in Tris buffer, 1:60 w/v, and centrifuged at 40,000 g for 10 minutes. This step was repeated twice more so that, in total, the brain tissue was homogenised and centrifuged four times. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.4 containing 300 mM sodium chloride and 5 mM potassium chloride (equivalent to 18.75 mg wet weight of tissue/ml) and used immediately in the binding assay. All centrifugations were performed at 4°C.

Membranes (400  $\mu$ l; equivalent to 7.5 mg wet weight of tissue/tube) were incubated with 50  $\mu$ l [ $^3$ H]nisoxetine at a single concentration of 0.6 nM and 50  $\mu$ l of distilled water (total binding) or 50  $\mu$ l of test compound (at a single concentration  $10^{-6}$  M or at 10 concentrations ranging from  $10^{-11}$ - $10^{-3}$  M) or 50  $\mu$ l of mazindol (1  $\mu$ M; non-specific binding) for 4 h at 4°C. Membrane bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM Tris-HCl, pH 7.4 containing 120 mM sodium chloride and 5 mM potassium chloride (wash setting 9,9,0). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

The ability of compounds of Formula I to interact with muscarinic receptors has been demonstrated for the products of Examples 1-56 by the following test which determines the ability of compounds to displace the standard ligand, [<sup>3</sup>H]N-methylscopolamine, from muscarinic receptors *in vitro*.

5

Frontal cortical tissue from the brains of male Charles River rats weighing 150-250 g was homogenised in ice-cold 20 mM HEPES buffer, pH 7.5 (measured at 25°C) containing 100 mM sodium chloride and 10 mM magnesium chloride (1:10 w/v) using a Polytron PT3100 (speed setting 21,700rpm, 3 x 5 seconds) and 10 centrifuged at 49,500 g for 30 minutes at 4°C. The supernatant was discarded and the pellet rehomogenised in 20 mM HEPES buffer, pH 7.5 containing 100 mM sodium chloride and 10 mM magnesium chloride (equivalent to 12.5 mg wet weight of tissue/ml). Membranes were stored at -80°C until required.

15

Membranes were thawed, diluted 1:10 in ice-cold 20 mM HEPES buffer, pH 7.5 containing 100 mM sodium chloride and 10 mM magnesium chloride and homogenised using a Polytron PT3100 as above. Diluted membranes (200 µl; equivalent to 0.25 mg wet weight of tissue/tube) were incubated with 200 µl of 20 mM HEPES buffer, pH 7.5 containing 100 mM sodium chloride and 10 mM magnesium chloride and 50 µl of [<sup>3</sup>H]N-methylscopolamine at a single concentration of 0.15 nM and 50 µl of distilled water (total binding) or 50 µl of test compound (at a single concentration of 10<sup>-6</sup> M or at 10 concentrations ranging from 10<sup>-11</sup>- 10<sup>-3</sup> M) or 50 µl of atropine sulphate (1 µM; non-specific binding) for 30 min at 30°C. Membrane bound radioactivity was recovered by filtration under vacuum through 25 Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 20 mM HEPES buffer, pH 7.5 (wash 1,2 at setting 5,5). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

30

For each of these tests measuring the ability of compounds of Formula I to displace standard ligands from 5-HT<sub>1A</sub> receptors and 5-hydroxytryptamine (5-HT) and noradrenaline (NA) reuptake sites and muscarinic receptors *in vitro*, the percentage displacement of specific binding of tritiated ligand by 10<sup>-6</sup> M test compound was calculated in the following way.

Firstly, specific binding of tritiated ligand in the absence (A) and presence (B) of test compound was determined:

In the absence of compound:

5

$$A \text{ (dpm)} = \text{Total binding (dpm)} - \text{Non-specific binding (dpm)}$$

In the presence of compound ( $10^{-6}$  M):

10

$$B \text{ (dpm)} = \text{Binding at } 10^{-6} \text{ M (dpm)} - \text{Non-specific binding (dpm)}$$

The specific binding of tritiated ligand in the presence (B) of compound was then converted to a percentage of specific binding of tritiated ligand in the absence (A) of compound:

15

$$\% \text{ Specific binding at } 10^{-6} \text{ M} = B \text{ (dpm)} / A \text{ (dpm)} \times 100$$

20 The percentage displacement of specific binding of tritiated ligand by the test compound ( $10^{-6}$  M) was then obtained by subtraction of the percentage specific binding in the presence of compound from the percentage specific binding in the absence of compound, which is taken as the maximum binding and so equals 100%:

$$\% \text{ Displacement at } 10^{-6} \text{ M} = 100 - \% \text{ Specific binding at } 10^{-6} \text{ M.}$$

25 In some cases, displacement curves were then produced for compounds which displaced  $\geq 50\%$  of specific binding of the tritiated ligand at  $10^{-6}$  M using a range of concentrations of the compound. The  $K_i$  was then calculated by fitting the following simultaneous equations (which are derived from the Feldman equations) by robust non-linear regression to data from three experiments simultaneously:

$$\begin{aligned}
 F_1 &= [L]_{T_{tot}} - B \\
 K_i' &= K_i \left( 1 + \frac{F_1}{K_d} \right) \\
 ab &= \frac{C_k r_1 - L + K_i'}{2} \\
 F_2 &= -ab + \sqrt{ab^2 + K_i' L} \\
 B &= \begin{cases} N_K F_1 & \text{Non-specific data} \\ \frac{C_k r_1 F_1}{K_d + F_1 + \frac{K_d F_2}{K_i}} + N_K F_1 & \text{Otherwise} \end{cases}
 \end{aligned}$$

where B is the concentration of bound ligand-receptor complex. This is calculated for each observation as:

5.  $B = \frac{DPM}{\text{Specific activity} \times \text{Volume of incubation}}$

L is the concentration of compound

$[L]_{tot}$  is the concentration of the tritiated ligand used, calculated as:

$$[L]_{tot} = \frac{\text{Mean DPM for Total DPM added samples} \times \text{Dilution}}{\text{Specific activity} \times \text{Volume of incubation}}$$

$K_d$  is the equilibrium dissociation constant for the ligand.

10.  $F_1$  and  $F_2$  are the concentrations of free ligand and free compound respectively.

$r_1$  is the total concentration of the receptor in the first experiment. This must be multiplied by  $C_K$  for subsequent experiments ( $C_1=1$ ).

$N_K$  is the non-specific binding constant.

15

The results obtained in the above tests for 5-HT1A binding and 5-HT and NA uptake, and muscarinic binding for the final products of Examples 1 – 56 hereinafter are given in Table 1 below.  $K_d$ s are in nM and are means of three independent determinations. % Figures are for % displacement at  $10^{-6}$  M for a single

20. determination.

TABLE 1

| Example No. | 5-HT1A | 5-HT uptake | NA uptake | Muscarinic |
|-------------|--------|-------------|-----------|------------|
| 1           | 51%    | 1%          | 58%       | 0%         |
| 2           | 13     | 398         | 3.7       | 19%        |
| 3           | 201    | 200         | 12        | 28%        |
| 4           | 26     | 72%         | 6.2       | 0%         |
| 5           | 11     | 162         | 3.1       | 16%        |
| 6           | 7.7    | 378         | 3.5       | 9%         |
| 7           | 18     | 492         | 8.9       | 338        |
| 8           | 79%    | 48%         | 85%       | 87%        |
| 9           | 114    | 119         | 17        | 17%        |
| 10          | 73%    | 19%         | 94%       | 16%        |
| 11          | 97%    | 8%          | 61%       | 39%        |
| 12          | 93%    | 18%         | 87%       | 54%        |
| 13          | 101    | 89          | 2.0       | 15         |
| 14          | 82%    | 39%         | 3.1%      | 16%        |
| 15          | 60     | 269         | 8.1       | 4%         |
| 16          | 27     | 510         | 3.8       | 418        |
| 17          | 16     | 162         | 2.7       | 10.4       |
| 18          | 2.0    | 14%         | 46        | 11%        |
| 19          | 59%    | 8%          | 57%       | 19%        |
| 20          | 5.0    | 623         | 9.3       | 420        |
| 21          | 62%    | 13%         | 93%       | 22%        |
| 22          | 93     | 283         | 2.2       | 49         |
| 23          | 27     | 71          | 1.1       | 63         |

| Example No. | 5-HT1A | 5-HT uptake | NA uptake | Muscarinic |
|-------------|--------|-------------|-----------|------------|
| 24          | 98     | 245         | 5.6       | 353        |
| 25          | 74%    | 34%         | 99%       | 51%        |
| 26          | 61%    | 57%         | 99%       | 33%        |
| 27          | 64%    | 43%         | 99%       | 49%        |
| 28          | 73%    | 48%         | 97%       | 48%        |
| 29          | 55%    | 42%         | 99%       | 35%        |
| 30          | 58%    | 42%         | 99%       | -5%        |
| 31          | 53%    | 62%         | 101%      | 28%        |
| 32          | 69%    | 54%         | 100%      | 36%        |
| 33          | 55%    | 48%         | 101%      | 28%        |
| 34          | 76     | 234         | 61        | 23%        |
| 35          | 36.5   | 347         | 2.2       | 245        |
| 36          | 62%    | 68%         | 104%      | 95%        |
| 37          | 189    | 30%         | 146       | 20%        |
| 38          | 50%    | 5%          | 84%       | 16%        |
| 39          | 73%    | 64%         | 64%       | 64%        |
| 40          | 75%    | 62%         | 44%       | 16%        |
| 41          | 2.9    | 110         | 7.5       | 28%        |
| 42          | 100%   | 65%         | 101%      | 31%        |
| 43          | 57%    | 60%         | 102%      | 99%        |
| 44          | 53%    | 4%          | 86%       | 32%        |
| 45          | 8.8    | 28          | 1.6       | 7.9        |
| 46          | 94%    | 92%         | 100%      | 88%        |
| 47          | 53%    | 65%         | 97%       | 39%        |
| 48          | 23     | 24.3        | 4.1       | 3.9        |

| Example No. | 5-HT1A | 5-HT uptake | NA uptake | Muscarinic |
|-------------|--------|-------------|-----------|------------|
| 49          | 77%    | 61%         | 102%      | 73%        |
| 50          | 98%    | 46%         | 82%       | 81%        |
| 51          | 2.1    | 251         | 17        | 39%        |
| 52          | 66%    | 86%         | 103%      | 97%        |
| 53          | 64%    | 71%         | 101%      | 100%       |
| 54          | 54%    | 97%         | 101%      | 2%         |
| 55          | 60%    | 85%         | 101%      | NT         |
| 56          | 61%    | 81%         | 101%      | 96%        |

Ki values are n=1, mean of n=2 or mean of n=3.

NT = Not tested.

5 The ability of compounds of the invention to inhibit monoamine oxidase A activity is demonstrable by the following test.

The assay was performed using the following general procedure in which the tissue source was human placenta:

10

| Enzyme   | Substrate           | Incubation | Reaction product | Method of detection |
|----------|---------------------|------------|------------------|---------------------|
| MAO-A(h) | Kynuramine (0.15mM) | 30min/30°C | 4-OHquinoline    | Spectrophotometry   |

The compounds were tested at 1 and 10micromolar in duplicate.

15 Ref: Weyler, W. and Salach, J.I. (1985) Purification and properties of mitochondrial monoamine oxidase type A from human placenta. J. Biol. Chem., 260: 13199-13207.

20 The combination of inhibition of monoamine oxidase activity and 5-HT reuptake inhibition may cause serotonin syndrome (Sternbach, H. Serotonin syndrome. Am. J. Psychiatry 148, 705-713, 1991) which is highly undesirable.

Acute feeding studiesAnimals and environment

5

Experiments were performed on male Sprague-Dawley rats (300-450 g at the start of the experiment) which were obtained from Charles River (Margate). Animals were individually-housed in polypropylene cages with metal grid floors at a temperature of  $21\pm1$  °C and 55% humidity. Polypropylene trays were placed below each cage. Animals were maintained on a reverse phase light-dark cycle. Lights were off from 09.30 h to 17.30 h during which time the room was illuminated by red light. Animals had free access to a powdered rat diet and tap water at all times. The diet was contained in glass feeding jars (10 cm diameter; 8 cm deep) with aluminium lids. Each lid had a hole (3 cm diameter) cut in it to allow access to the food.

10 Animals were accustomed to these conditions for at least two weeks before experimentation.

15

Test procedure

20

On the day prior to testing, the animals were randomly allocated to treatment groups containing 6-8 rats, weighed and their food intakes over a 6 h period were measured. These baseline readings were taken to ensure that the body weights and food intakes of the different groups of rats were not significantly different before drug treatment. On the test day, animals were given vehicle or one of three doses of the test drug. All drugs were dosed orally at the onset of the dark phase since rats consume most of their food during this period. Feeding jars were weighed (to the nearest 0.1g) at the time of drug administration and 1, 2, 4, 6 and 24 h after dosing. At each reading, the trays below the cages were examined for spilt food which was then returned to the feeding jar. However, spillage of food from the feeding jars was generally negligible.

25

30

All drug doses are expressed as the free base. Drugs were dissolved in deionised water or suspended in 0.4% cellosolve using a sonic bath.

Data analysis

Variations in body weight were accounted for by expressing the results as g/kg rat weight (treatment group means  $\pm$  s.e.mean). ED<sub>50</sub> values (the dose of a drug required to reduce food intake to 50% of the control values) were calculated from a logistic sigmoid curve using a dedicated computer program. Statistical comparisons between mean group intakes were made using analysis of variance and Dunnett's test (two-tailed).

Especially preferred compounds of Formula Ia have surprisingly lower affinity for muscarinic receptors compared to the Examples of WO97/02269 and/or have significantly reduced MAO<sub>A</sub> inhibitory activity compared to compounds exemplified in WO97/02269. For example, Example 1 of WO97/02269 has a muscarinic receptor binding K<sub>i</sub> of 130 nM. Muscarinic affinity may cause undesired side-effects, for example dry mouth, blurred vision, sweating, palpitations, constipation and aggravation of narrow angle glaucoma (Blackwell, B. Adverse effects of antidepressant drugs. Part 1 Monoamine oxidase inhibitors and tricyclics. Drugs 21, 202-219, 1981). Obviously it is desirable for compounds to have minimal affinity for muscarinic receptors.

Particularly preferred compounds of the present invention have superior activity in acute feeding studies compared to the compounds exemplified in WO 97/02269.

The invention is illustrated by the following Examples which are given by way of example only. The final product of each of these Examples was characterised by one or more of the following procedures: high performance liquid chromatography; elemental analysis, nuclear magnetic resonance spectroscopy, mass spectroscopy and infrared spectroscopy.

30

ExamplesExample 1

Triethylamine (75 ml) was added dropwise at < 10 °C to a stirred suspension of 3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (50 g;

prepared in a manner similar to that described in WO 97/02269) in dichloromethane (400 ml), then the mixture was stirred at ambient temperature for 1 hour. Water (300 ml) was added, then the organic phase was separated, washed with water (2 x 100 ml) and saturated aqueous sodium chloride solution (100 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole as a pale yellow solid (34 g) which was used without further purification.

10     *n*-Butyllithium (2.5 M solution in hexanes; 17.5 ml) was added dropwise under nitrogen at -70 °C to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (10.14 g) in tetrahydrofuran (260 ml), then the mixture was stirred at -70 °C for 20 minutes, allowed to warm to 0 °C, and stirred at 0 °C for 30 minutes. Dimethylformamide (2.86 ml) was added, and the mixture was stirred at ambient temperature for 20 minutes. Saturated aqueous sodium chloride solution (200 ml) and ether (400 ml) were added, then the organic phase was separated, washed with water (100 ml) and saturated aqueous sodium chloride solution (100 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 10:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents removed *in vacuo*. The residue was heated under reflux for 5 minutes with propan-2-ol (100 ml), then the mixture was filtered while hot and allowed to cool to ambient temperature. The resulting solid was collected by filtration and dried *in vacuo* at 60 °C to give 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a yellow solid (1.4 g), m.p. 206 °C.

25

### Example 2

30     A mixture of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.198 g), sodium borohydride (0.026 g) and methanol (20 ml) was stirred at ambient temperature under nitrogen for 1 hour; then water (2 ml) was added and the mixture was concentrated *in vacuo* to remove methanol. The residue was partitioned between water (30 ml) and ethyl acetate (50 ml), then the organic phase was separated, washed with saturated aqueous sodium chloride solution (20 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was removed *in vacuo* to leave [3-

(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol as a yellow solid (0.077 g), m.p. 168 - 170 °C.

5    Example 3

A mixture of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.44 g), hydroxylamine hydrochloride (0.118 g) and ethanol (30 ml) was heated under reflux for 2.75 hours, then cooled to ambient temperature. The 10 resulting solid was collected by filtration and suspended in dichloromethane (50 ml). Triethylamine (3 ml) was added, then the resulting solution was washed with water (20 ml) and saturated aqueous sodium chloride solution (20 ml), dried ( $MgSO_4$ ), and the solvent was removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde oxime as a white solid (0.07 g), 15 m.p. 226-228°C.

Example 4

20       Methylmagnesium bromide (3 M solution in ether, 1.2 ml) was added dropwise at 0°C under nitrogen to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.286 g) in tetrahydrofuran (30 ml), then the mixture was stirred at ambient temperature for 15 minutes. Water (5 ml) and ethyl acetate (70 ml) were added, then the organic phase was separated, 25 washed with water (20 ml) and saturated aqueous sodium chloride solution (20 ml), dried ( $Na_2SO_4$ ), and the solvents were removed *in vacuo*. The residue was triturated with ether (30 ml) and the resulting solid was collected by filtration and dried *in vacuo* at 100°C to give 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-ethanol as an off-white solid (0.213 g), m.p. 174-176°C.

30

Example 5

A suspension of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (0.5 g) in ethanol (25 ml) was heated under reflux until all of the solid 35 had dissolved. Ethereal hydrogen chloride solution (1 M; 2 ml) was added, then the mixture was heated under reflux for 3 minutes and allowed to cool to ambient

temperature. The resulting solia was collected by filtration, washed with ether (20 ml) and dried *in vacuo* at 60°C to give 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-methanol hydrochloride as a white solid (0.32 g), m.p. 240-250°C (decomposes). Ethereal hydrogen chloride solution (1 M; 2 ml) was 5 added to the filtrate remaining from isolation of the above solid, and the mixture was stirred at ambient temperature for 18 hours. The resulting solid was collected by filtration, washed with ether (20 ml) and dried *in vacuo* at 60°C to give a second crop of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol hydrochloride as a white solid (0.1 g), m.p. 240-250°C (decomposes).

10

Example 6

A mixture of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (200 g; prepared in a manner similar to that described in 15 WO 97/02269), saturated aqueous sodium carbonate solution (1000 ml) and dichloromethane (2000 ml) was stirred vigorously at ambient temperature for 1.5 hours, then the organic layer was separated, washed with water (500 ml), dried (MgSO<sub>4</sub>) and the solvent was removed *in vacuo*. The process was repeated on the same scale, and the two products were combined to give 3-(benzo[*b*]thiophen-3-yl)- 20 5,6-dihydroimidazo[2,1-*b*]thiazole as a pale yellow solid (264.3 g), which was used without further purification.

Bromine (55.5 ml) was added dropwise at 0-5 °C over 1.75 hours to a stirred 25 solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (264.3 g) in dichloromethane, then the mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1 hour. The resulting solid was collected by filtration, washed with dichloromethane (300 ml) and dried *in vacuo* at 70°C to give 3-(benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a pale yellow solid (431 g) which was used without further purification.

30

3-(Benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (170 g) was added in portions under nitrogen at 0-8°C over 1 hour to a stirred solution of ethylmagnesium chloride [2.0 M solution in ether (620 ml)] in tetrahydrofuran (1700 ml), then the mixture was stirred at 3°C for 1.5 hours. 35 Dimethylformamide (136 ml) was added at 3-8 °C over 30 minutes, then the mixture

was stirred at ambient temperature for 2 hours, cooled to 8°C and quenched by the cautious addition of saturated aqueous ammonium chloride solution (600 ml) and water (350 ml). Ethyl acetate (1500 ml) was added, the mixture was stirred at ambient temperature for 18 hours, and the resulting solid (Fraction 1) was collected by filtration. The organic layer of the filtrate was separated, washed with saturated aqueous sodium chloride solution (500 ml), dried ( $MgSO_4$ ), and the solvents were removed *in vacuo*. The residue was dissolved in hot propan-2-ol (1000 ml) and the solution was filtered while hot then allowed to stand at ambient temperature for 20 hours. The resulting solid was collected by filtration, washed with propan-2-ol (100 ml) and dried *in vacuo* at 70°C to give 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a yellow solid (19.4 g), m.p. 206°C. A mixture of the solid Fraction 1, dichloromethane (2100 ml), 2 M hydrochloric acid (250 ml) and water (1000 ml) was stirred at ambient temperature for 15 minutes, then triethylamine (80 ml) was added. The dichloromethane layer was separated, and further product was isolated from the aqueous layer by extraction into dichloromethane (500 ml). The combined dichloromethane solutions were dried ( $MgSO_4$ ), and the solvent was removed *in vacuo* to give further 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a yellow solid (63.0 g), m.p. 208°C.

20

Sodium borohydride (12.5 g) was added in portions over 10 minutes to an ice-cold stirred suspension of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (63 g) in methanol (1200 ml), then the mixture was stirred at 5°C for 30 minutes, at ambient temperature for 4 hours, and at reflux temperature for 20 minutes. The mixture was cooled to ambient temperature over 1 hour then water (200 ml) was added and stirring at ambient temperature was continued for 1 hour. The resulting solid was collected by filtration, washed with water (200 ml), ethanol (200 ml) and ether (200 ml), then dried *in vacuo* at 60°C to give [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol as an off-white solid (52.1 g) which was used without purification.

30  
A stirred suspension of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (52.1 g) in methanol (2200 ml) was heated under reflux until virtually all of the solid had dissolved. The heat source was removed, and a solution 35 of fumaric acid (21 g) in methanol (250 ml) was added over 1 minute. The mixture

was stirred for 10 minutes and allowed to stand at ambient temperature for 1 hour, then it was cooled in ice for 3 hours. The resulting solid was collected by filtration, washed with ice-cold methanol (200 ml), and dried *in vacuo* at 60°C for 3 hours and at 80°C for 2 hours to give a white solid which was shown by nmr spectroscopy to be  
5 solvated by 1 equivalent of methanol. This solid was combined with a second sample of product (5.2 g; also solvated by methanol) prepared in a manner similar to that described above, and the combined material was ground using a pestle and mortar, then dried *in vacuo* at 90°C and 133Pa for 15 hours to give [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol fumarate  
10 (solvated by 0.05 equivalent of methanol) as a white solid (53.4 g), m.p. 258-262°C (decomposes).

Example 7

15 Phenyltrimethylammonium tribromide (3.0 g) was added in portions under nitrogen at 0°C to a stirred suspension of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (2.0 g) in tetrahydrofuran (50 ml), then the mixture was stirred at 0°C for 1 hour and at ambient temperature for 18 hours. Water (50 ml) and triethylamine (50 ml) were added, and the organic phase was separated, washed  
20 with saturated aqueous sodium chloride solution (50 ml), dried ( $MgSO_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 9:1 mixture of ethyl acetate and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole, as a yellow  
25 solid (1.0 g), m.p. 196-200°C.

Example 8

Phenyltrimethylammonium tribromide (0.75 g) was added in portions under  
30 nitrogen at 0°C to a stirred suspension of 3-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (0.5 g; prepared in a manner similar to that described in WO 97/02269)) in tetrahydrofuran (15 ml), then the mixture was stirred at 0°C for 4 hours and allowed to warm to ambient temperature. Water (50 ml) and triethylamine (50 ml) were added, and the organic phase was separated, washed with saturated  
35 aqueous sodium chloride solution (50 ml), dried ( $MgSO_4$ ), and the solvents were

removed *in vacuo*. The residue was purified by flash chromatography over silica using a 9:1 mixture of ethyl acetate and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-2-bromo-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine as a pale yellow solid (0.2 g), m.p. 200-202°C.

Example 9

Sodium hydride (60% dispersion in mineral oil; 1.35 g) was added in portions at ambient temperature under nitrogen to a stirred solution of 3-acetyl-benzo[*b*]thiophen (2.9 g) in diethyl carbonate (50 ml), then the mixture was stirred at 80°C for 1.5 hours and poured onto a mixture of water (300 ml) and acetic acid (5 ml). The product was extracted into ether (3 x 150 ml), then the combined extracts were washed with water (2 x 50 ml) and saturated aqueous sodium chloride solution (50 ml), dried ( $MgSO_4$ ), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using a 9:1 mixture of hexane and ethyl acetate as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave ethyl 3-(benzo[*b*]thiophen-3-yl)-3-oxopropanoate as a brown oil (1.5 g) which was used without further purification.

Phenyltrimethylammonium tribromide (2.15 g) was added in portions at 0°C under nitrogen to a stirred solution of ethyl 3-(benzo[*b*]thiophen-3-yl)-3-oxopropanoate (1.5 g) in tetrahydrofuran (30 ml); then the mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1.5 hours. The resulting solid was removed by filtration and washed with tetrahydrofuran (30 ml). The filtrate and washings were combined and the solvent was removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using a 9:1 mixture of petroleum ether (b.p. 60-80 °C) and ethyl acetate as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave ethyl 3-(benzo[*b*]-thiophen-3-yl)-2-bromo-3-oxopropanoate as a brown solid (1.7 g), m.p. 81-83°C.

A mixture of ethyl 3-(benzo[*b*]thiophen-3-yl)-2-bromo-3-oxopropanoate (1.7 g), 2-imidazolidinethione (0.53 g) and ethanol (30 ml) was heated under reflux for 10 minutes, then acetic acid (15 ml) was added and the mixture was heated

under reflux for 18 hours. The solvents were removed *in vacuo* and the residue was triturated with ethanol (20 ml). The resulting solid was collected by filtration, washed with ethanol (10 ml) and ether (20 ml), then dried *in vacuo* at 60°C to give ethyl 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxylate as an off-white solid (1.15 g), m.p. 209-211°C.

5 A mixture of ethyl 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxylate (0.4 g), triethylamine (2 ml) and dichloromethane (15 ml) was stirred at ambient temperature for 20 minutes, then it was diluted with 10 dichloromethane (40 ml), washed with water (2 x 20 ml) and saturated aqueous sodium chloride solution (20 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue (0.22 g) was dissolved in tetrahydrofuran (7 ml), and methylmagnesium bromide (3 M solution in ether; 0.66 ml) was added under nitrogen. The mixture was stirred at ambient temperature for 2 hours, then further 15 methylmagnesium bromide (3 M solution in ether; 0.42 ml) and toluene (5 ml) were added. The mixture was stirred at ambient temperature for 5 minutes and at 90-95°C for 5 hours; then it was cooled to ambient temperature and diluted with water (30 ml). The product was extracted into ethyl acetate (2 x 30 ml), and the combined extracts were washed with water (30 ml) and saturated aqueous sodium 20 chloride solution (30 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. A mixture of the residue, fumaric acid (0.037 g) and ethanol (5 ml) was heated under reflux for 5 minutes, then the hot solution was decanted from a small trace of undissolved solid and allowed to cool to ambient temperature. The resulting solid was collected by filtration, washed with ether (10 ml) and dried *in vacuo* at 60°C to 25 give 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-methyl-ethanol fumarate as an off-white solid (0.057 g), m.p. 180-182°C.

#### Example 10

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Ethylmagnesium chloride (2M solution in ether; 1.4 ml) was added dropwise at ambient temperature to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]-thiazole-2-carboxaldehyde (0.52 g) in tetrahydrofuran (30 ml), then the mixture was stirred at ambient temperature for 30 minutes. Further 35 ethylmagnesium chloride (2M solution in ether; 0.5 ml) was added, the mixture was stirred at ambient temperature for 1 hour, then it was quenched by the addition of

water (30 ml). The product was extracted into ether (50 ml) followed by ethyl acetate (2 x 50 ml), then the combined extracts were washed with saturated aqueous sodium chloride solution (2 x 30 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage 5 Flash 40i ® equipment using a 99:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents removed *in vacuo* to leave 1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]propan-1-ol as an orange solid (0.24 g), m.p. 92-94°C.

10 Example 11

Triethylamine (50 ml) was added dropwise at ambient temperature to a stirred suspension of 3-(5-methoxybenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (1 g; prepared in a manner similar to that described in 15 WO 97/02269) in dichloromethane (25 ml), then the mixture was stirred at ambient temperature for 10 minutes. Water (25 ml) was added, then the organic phase was separated, washed with water (25 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo* to leave 3-(5-methoxybenzo[b]thiophen-3-yl)-5,6-dihydro-20 imidazo[2,1-*b*]thiazole as a brown solid (0.65 g) which was used without further purification.

Phenyltrimethylammonium tribromide (1.5 g) was added in portions at 0°C under nitrogen to a stirred solution of 3-(5-methoxybenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (0.65 g) in tetrahydrofuran (25 ml), the mixture was 25 stirred at 0°C for 16 hours, then it was allowed to warm to ambient temperature. Triethylamine (50 ml) and water (50 ml) were added, then the organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 99:1:0.1 mixture of ethyl acetate, methanol and triethylamine as eluant. Appropriate fractions were combined 30 and the solvents were removed *in vacuo*. The residue was crystallised from methanol and the resulting solid was collected by filtration and dried *in vacuo* at ambient temperature to give 2-bromo-3-(5-methoxybenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole as an off-white solid (0.05 g), m.p. 210°C (decomposes).

Example 12

Phenyltrimethylammonium tribromide (1.0 g) was added in portions at 0 – 5 °C under nitrogen over 15 minutes to a stirred solution of 3-(5-chlorobenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (0.8 g; prepared in a manner similar to that described in WO 97/02269) in tetrahydrofuran (20 ml), then the mixture was stirred at ambient temperature for 18 hours. Water (30 ml) and triethylamine (5 ml) were added, then the product was extracted into dichloromethane (2 x 20 ml), and the combined extracts were washed with water (4 x 20 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo* to leave 2-bromo-3-(5-chlorobenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole as a yellow solid (0.72 g), m.p. 205 – 208°C (decomposes).

15 Example 13

A mixture of 3-acetylbenzo[b]thiophene (25 g), dimethylamine hydrochloride (15.05 g), paraformaldehyde (5.7 g), concentrated hydrochloric acid (1 ml) and ethanol (75 ml) was heated under reflux for 18 hours then allowed to cool to ambient temperature. The resulting solid was collected by filtration and dried *in vacuo* at ambient temperature to give 1-(benzo[b]thiophen-3-yl)-3-(dimethylamino)propan-1-one hydrochloride as a pink solid (15.7 g), m.p. 169 – 171°C. The solvent was removed *in vacuo* from the filtrate, and the residue was triturated with ether (100 ml). The resulting solid was collected by filtration and dried *in vacuo* at ambient temperature to give a second crop of 1-(benzo[b]thiophen-3-yl)-3-(dimethylamino)-propan-1-one hydrochloride as a pink solid (13.8 g).

A mixture of 1-(benzo[b]thiophen-3-yl)-3-(dimethylamino)propan-1-one hydrochloride (29.4 g) and water (600 ml) was basified to pH 9.0 by the addition of saturated aqueous sodium carbonate solution, the mixture was stirred at ambient temperature for 1 hour, then the free base was extracted into ether (3 x 100 ml). The combined extracts were dried ( $\text{MgSO}_4$ ) and the solvent was removed *in vacuo*. The residue was dissolved in methanol (50 ml), then the solution was cooled in ice, and iodomethane (15.7 ml) was added dropwise. The mixture was stirred at ambient temperature for 1 hour, then the resulting solid was collected by filtration, washed well with ether, and dried *in vacuo* at ambient temperature to give [3-(benzo[b]-

thiophen-3-yl)-3-oxopropyl]trimethylammonium iodide as a pink solid (28.7 g), m.p. 165 – 167°C.

A mixture of [3-(benzo[b]thiophen-3-yl)-3-oxopropyl]trimethylammonium iodide (5.0 g), sodium hydrogencarbonate (5.0 g), ether (150 ml) and water (130 ml) was stirred at ambient temperature for 4 hours, then the product was extracted into ether (3 x 150 ml). The combined extracts were dried ( $MgSO_4$ ) and the solvent was removed *in vacuo* to leave 1-(benzo[b]thiophen-3-yl)propanone as a pink solid (2.1 g) which was used without further purification.

10

A solution of 1-(benzo[b]thiophen-3-yl)propanone (0.75 g) and benzyl alcohol (0.41 ml) in dichloromethane (2 ml) was cooled to 0°C, and concentrated sulphuric acid (2 drops) was added. The mixture was stirred at 0°C for 3 hours, then allowed to stand at 4°C for 18 hours. Further benzyl alcohol (0.82 ml) was added, the mixture was stirred at 0°C for 7 hours, then it was diluted with dichloromethane (20 ml), washed with saturated aqueous sodium hydrogencarbonate solution (2 x 10 ml) and water (10 ml), and dried ( $MgSO_4$ ). The solvent was removed *in vacuo*, and the residue was purified by preparative-scale thin layer chromatography on a silica-coated glass plate using dichloromethane as eluant. Appropriate sections of silica were removed from the developed plate, and the product was extracted by trituration with dichloromethane (30 ml). The extract was filtered, and the solvent removed *in vacuo* to leave 1-(benzo[b]thiophen-3-yl)-3-benzylxypropan-1-one as an orange oil (0.49 g) which was used without further purification.

25

Phenyltrimethylammonium tribromide (0.4 g) was added in portions under nitrogen to a stirred solution of 1-(benzo[b]thiophen-3-yl)-3-benzylxypropan-1-one (0.43 g) in tetrahydrofuran (5 ml), the mixture was stirred at ambient temperature for 18 hours, then it was filtered and the solvent was removed *in vacuo* to leave 1-(benzo[b]thiophen-3-yl)-3-benzylxy-2-bromopropan-1-one as a yellow oil (0.56 g) which was used without further purification.

30

A mixture of 1-(benzo[b]thiophen-3-yl)-3-benzylxy-2-bromopropan-1-one (0.54 g), 2-imidazolidinethione (0.15 g), ethanol (3 ml) and acetic acid (1 ml) was heated under reflux under nitrogen for 18 hours, then the solvents were removed *in vacuo*. The residue was triturated with ice-cold ethanol (5 ml) and the resulting solid

was collected by filtration, washed with ethanol (5 ml), and dried *in vacuo* at 60°C to give 3-(benzo[*b*]thiophen-3-yl)-2-ethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a cream solid (0.19 g), m.p. > 250°C.

5 Example 14

Vinylmagnesium chloride (1 M solution in tetrahydrofuran; 6.7 ml) was added dropwise at 0°C under nitrogen to a stirred suspension of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.64 g) in tetrahydrofuran (30 ml), then the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 30 minutes. Water (50 ml) was added, and the mixture was concentrated *in vacuo* to remove tetrahydrofuran, then the product was extracted into ethyl acetate (3 x 30 ml). The combined extracts were washed with saturated aqueous sodium chloride solution (2 x 25 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using 1 – 5% mixtures of methanol in dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-en-1-ol as a pale yellow foam (0.12 g), m.p. 60–65°C.

20

Example 15

1-Propynylmagnesium bromide (0.5 M solution in ether; 10.5 ml) was added dropwise at 0°C under nitrogen to a stirred suspension of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.5 g) in tetrahydrofuran (30 ml), then the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 30 minutes. Water (60 ml) and ethyl acetate (100 ml) were added, then the organic phase was separated, washed with saturated aqueous sodium chloride solution (2 x 25 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using 1 – 5% mixtures of methanol in dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-2-yn-1-ol as a white solid (0.11 g), m.p. 190 – 200°C (decomposes).

Example 16

*n*-Butyllithium (2.5 M solution in hexanes; 4.7 ml) was added dropwise at 0°C under nitrogen to a stirred solution of methyltriphenylphosphonium bromide (4.2 g) in tetrahydrofuran (30 ml), then the mixture was stirred at 0°C for 5 minutes and at ambient temperature for 30 minutes. 3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (3.05 g) was added in portions, then the mixture was heated under reflux for 3 hours and allowed to cool to ambient temperature. Ethyl acetate (75 ml) and water (50 ml) were added, then the organic phase was separated, washed with saturated aqueous sodium chloride solution (50 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was diluted with 2.5 M hydrochloric acid (75 ml), the mixture was stirred at ambient temperature for 3 hours, then it was filtered to remove a gummy semisolid. The filtrate was shaken with ethyl acetate (25 ml), then the organic phase was separated, dried ( $\text{MgSO}_4$ ), and the solvent was removed *in vacuo* to leave slightly impure 3-(benzo[*b*]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride as a white solid (0.85 g). Further product was isolated by extraction with dichloromethane (2 x 50 ml), drying ( $\text{MgSO}_4$ ), and removal of the solvent *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride as a white solid (0.49 g), m.p. 221 – 223°C.

Example 17

3-(Benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (2 g) was added in portions under nitrogen at 0 – 5°C over 10 minutes to a stirred solution of ethylmagnesium chloride (2 M solution in ether; 7.2 ml) in tetrahydrofuran (20 ml), then the mixture was stirred at 0 – 5°C for 30 minutes. Allyl bromide (0.87 ml) was added dropwise, the mixture was stirred at ambient temperature for 18 hours, then it was quenched by the addition of saturated aqueous ammonium chloride solution (15 ml) followed by water (10 ml). The product was extracted into ethyl acetate (50 ml), then the extract was washed with water (25 ml) and saturated aqueous sodium chloride solution (25 ml), dried ( $\text{MgSO}_4$ ), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography over silica using 5 – 7% mixtures of methanol in dichloromethane as eluant. Appropriate fractions were combined and the solvents removed *in vacuo* to give a

brown gum (0.36 g). The gum was dissolved in ethanol (2 ml), and a solution of fumaric acid (0.13 g) in ethanol (2 ml) was added. The resulting solid was collected by filtration, washed with ethanol (10 ml) and dried *in vacuo* at 75°C to give 2-allyl-3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole fumarate as an off-white 5 solid (0.22 g), m.p. 163 – 164°C.

Example 18

*n*-Butyllithium (2.5 M solution in hexanes; 1 ml) was added dropwise under 10 nitrogen at -70°C over 10 minutes to a stirred solution of 3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (0.5 g; prepared in a manner similar to that described in WO 97/02269) in tetrahydrofuran (6 ml), then the mixture was stirred at -70°C for 30 minutes. Dimethylformamide (0.2 ml) was added, the mixture was stirred at -70°C for 5 minutes, then it was allowed to warm to ambient temperature. Saturated 15 aqueous ammonium chloride solution (30 ml) was added, and the product was extracted into dichloromethane (3 x 30 ml). The combined extracts were washed with water (30 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 9:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined, and 20 the solvents were removed *in vacuo* to leave 3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a brown solid (0.24 g), m.p. 192 - 195°C.

3-(Benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde 25 (0.17 g) was dissolved in methanol (6 ml) by gentle warming, then sodium borohydride (0.035 g) was added and the mixture was stirred at ambient temperature for 30 minutes. Water (50 ml) was added, the mixture was stirred at ambient temperature for 1 hour, then the resulting solid was collected by filtration, washed with water (10 ml) and dried *in vacuo* at 60°C to give [3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol 30 as a white solid (0.08 g), m.p. 184 - 187°C.

Example 19

A stirred mixture of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]-thiazole-2-carboxaldehyde (0.5 g), isopropylamine (1 ml), ethanol (50 ml) and acetic acid (1 drop) was heated under reflux for 4 hours, then the solvent was removed *in vacuo*. The residue was triturated with ether (30 ml), and the resulting solid was collected by filtration, washed with ether (10 ml) and dried *in vacuo* at ambient temperature to give *N*-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-ylmethylidene]-1-methylethylamine as a pale brown solid (0.38 g), m.p. 180-182°C.

10

Example 20

Benzyltrimethylammonium chloride (8 g) was added in portions at ambient temperature to a stirred solution of iodine trichloride (10 g) in dichloromethane (120 ml), then the mixture was stirred at ambient temperature for 2.5 hours. The resulting solid was collected by filtration and dried *in vacuo* at ambient temperature to give benzyltrimethylammonium tetrachloroiodate as a yellow solid (16.2 g) which was used without further purification.

20

Benzyltrimethylammonium tetrachloroiodate (5 g) was added in portions at 0°C over 10 minutes to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (3 g) in acetone (125 ml), then the mixture was stirred at 0°C for 1 hour. The resulting solid was collected by filtration, triturated with hot propan-2-ol (150 ml) and crystallised from ethanol (150 ml) to give an off-white solid (0.74 g).

25

Concentration of the mother liquor to 75 ml gave a second crop of solid (0.41 g). The two crops of solid were combined, triturated with hot ethanol (40 ml), and the resulting solid was collected by filtration, washed with ethanol (10 ml) and dried *in vacuo* at 60°C to give 3-(benzo[*b*]thiophen-3-yl)-2-chloro-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride 0.5 hydrate as an off-white solid (0.91 g), m.p. 255-257°C.

30

Example 21

3-(Benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (6 g) was added in portions under nitrogen at 0-5°C over 10 minutes to a stirred solution of ethylmagnesium chloride (2 M solution in ether; 21.6 ml) in tetrahydrofuran (100 ml), then the mixture was stirred at 0-5°C for 1 hour. This

mixture was added over 10 minutes at 50 - 70°C to a stirred solution of *N*-methoxy-*N*-methylacetamide (5 g) in tetrahydrofuran (50 ml), then stirring at 70°C was continued for a further 2.5 hours. The mixture was cooled in ice, then saturated aqueous ammonium chloride solution (100 ml), water (100 ml) and ethyl acetate (150 ml) were added. The organic layer was separated, washed with a mixture of saturated aqueous sodium chloride solution (100 ml) and water (100 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was triturated with ether (3 x 50 ml), and the resulting solid was collected by filtration, washed with ether (30 ml) and dried *in vacuo* to give a yellow solid (1.84 g). A sample (0.25 g) of the solid was crystallised from ethanol (3.5 ml), and the resulting solid was collected by filtration, washed with ethanol (5 ml), and dried *in vacuo* at 75°C to give 2-acetyl-3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole as a yellow solid (0.043 g), m.p. 203 - 205°C.

15    Example 22

Sodium hydride (60% dispersion in mineral oil; 0.15 g) was added in portions at ambient temperature over 10 minutes to a stirred suspension of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (1 g) in dimethylformamide (20 ml), then the mixture was stirred at ambient temperature for 45 minutes. Iodomethane (240  $\mu\text{l}$ ) was added, and stirring at ambient temperature was continued for a further 2 hours. Water (25 ml) and ethyl acetate (50 ml) were added, then the organic phase was separated, washed with water (4 x 25 ml) and saturated aqueous sodium chloride solution (25 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using 5-8% mixtures of methanol in dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo*. The residue was dissolved in warm ethanol (3 ml), added to a solution of fumaric acid (0.085 g) in warm ethanol (2 ml), and the mixture was allowed to cool to ambient temperature. The resulting solid was collected by filtration, washed with ethanol (3 ml), and dried *in vacuo* at 75°C to give 3-(benzo[*b*]thiophen-3-yl)-2-(methoxymethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole fumarate as a white solid (0.23 g), m.p. 175-176°C.

Example 23

3-(Benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (5 g) was added in portions under nitrogen at 0-5°C over 30 minutes to a 5 stirred solution of ethylmagnesium chloride [2.0 M solution in ether (15 ml)] in tetrahydrofuran (75 ml), then the mixture was stirred at ambient temperature for 1 hour. The mixture was cooled to 0 °C, dimethyl disulphide (1.8 ml) was added, then the mixture was stirred at ambient temperature for 24 hours, and quenched by the cautious addition of saturated aqueous ammonium chloride solution (50 ml). The 10 product was extracted into ethyl acetate (150 ml), then the extract was washed with water (50 ml) and saturated aqueous sodium chloride solution (50ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using a 19:1 mixture of ethyl acetate and methanol as eluant. Appropriate fractions were 15 combined and the solvents were removed *in vacuo*. The residue was triturated with ether (20 ml) and the resulting solid was collected by filtration and dried *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-2-(methylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole (1.9g) as an off-white solid, m.p. 129 – 131 °C.

Example 24

*n*-Butyllithium (2.5 M solution in hexanes; 1.7 ml) was added under nitrogen to an ice-cold, stirred suspension of methyltriphenylphosphonium bromide (1.5 g) in tetrahydrofuran (25 ml), then the mixture was stirred at ambient temperature for 30 25 minutes. A solution of 2-acetyl-3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (1.6 g) in tetrahydrofuran (15 ml) was added, the mixture was heated under reflux for 4h, allowed to stand at ambient temperature for 18 hours, then it was quenched by the addition of water (50 ml). The product was extracted into ethyl acetate (50 ml), then the extract was washed with saturated aqueous sodium 30 chloride solution (50 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using 5-6% mixtures of methanol in dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-2-(1-methylvinyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (0.14 g) as a brown solid, m.p. 76 °C.

Examples 25-33

Examples 25 - 33 were prepared as part of a High Speed Analogue library using the following general method :

5.

The appropriate commercially-available Grignard reagent (3 molar equivalents) was added to a solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (approximately 50 mg) in tetrahydrofuran (4 ml), the mixture was stirred at ambient temperature for 1 hour, water (1 ml) was added, then the mixture was left exposed to the atmosphere for 18 hours to allow the solvent to evaporate. Dichloromethane (4 ml) was added and the solution was pipetted onto a ChemElute (CE 1103; pH9) cartridge, allowed to stand for 15 minutes, then the product was eluted from the cartridge with dichloromethane (3 x 4 ml). The solvent was removed *in vacuo* to leave the required product which was analysed by high performance liquid chromatography on a Hypersil BDS C18 column (100 x 4.6mm) using gradient elution with mixtures of acetonitrile and 0.1M ammonium acetate buffer according to the following time schedule:

| Time (minutes) | Acetonitrile (%) | Ammonium acetate (%) |
|----------------|------------------|----------------------|
| 0              | 10               | 90                   |
| 8 - 9          | 100              | 0                    |
| 11             | 10               | 90                   |

20 All of the products of the following Examples gave satisfactory mass spectra : Hplc retention time and % purity are reported for each Example.

Example 25

25 1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylpropan-1-ol (Retention time: 3.28 minutes – Purity: 80%).

Example 26

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]butan-1-ol  
(Retention time: 3.29 minutes – Purity: 100%).

5

Example 27

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylbut-3-en-1-ol (Retention time: 3.42 minutes – Purity: 100%).

10

Example 28

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-3-methylbutan-1-ol (Retention time: 3.61 minutes – Purity: 90%).

15

Example 29

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pentan-1-ol  
(Retention time: 3.68 minutes – Purity: 100%).

20

Example 30

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-yn-1-ol  
(Retention time: 2.71 minutes – Purity: 100%).

25

Example 31

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-en-1-ol  
(Retention time: 3.12 minutes – Purity: 96%).

30

Example 32

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylprop-2-en-1-ol (Retention time: 3.13 minutes – Purity: 97%).

35

Example 33

1-[3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pent-4-en-1-ol

(Retention time: 3.44 minutes – Purity: 85%).

5

Example 34

In a manner similar to that described in Example 4, 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (prepared via the methodology 10 described in Example 6) was reacted with 2-methoxyphenylmagnesium bromide and the product was recrystallised from a mixture of methanol and propan-2-ol to give [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl](2-methoxyphenyl)-methanol as a white solid, m.p. 195 – 197 °C.

15    Example 35

*n*-Butyllithium (2.5M solution in hexanes; 73.8 ml) was added dropwise over 45 minutes at 0 – 4 °C under nitrogen to a stirred mixture of methyltriphenylphosphonium bromide (65.7 g) and tetrahydrofuran (680 ml), then the mixture was stirred at 4 °C for 10 minutes and at ambient temperature for 30 20 minutes. 3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (48 g; prepared in a manner similar to that described in Example 6) was added in portions at ambient temperature, then the mixture was heated under reflux for 3 hours, cooled to ambient temperature, and added to water (500 ml). The product was extracted into ethyl acetate (3 x 400 ml); then the combined extracts 25 were washed with water (400 ml), dried ( $MgSO_4$ ), and the solvents were removed *in vacuo*. The residue was triturated with ethyl acetate (300 ml) and the resulting solid was collected by filtration and recrystallised from ethyl acetate to give an off-white solid. The liquors from the trituration and recrystallisation were combined and concentrated to give a further crop of solid. This was repeated until no further solid 30 was isolable. All of the crops of solid were combined and repeatedly recrystallised from ethyl acetate until >99% pure (by hplc) to give 3-(benzo[*b*]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole as an off-white solid (43.5 g). The majority of the solid (41 g) was dissolved in warm methanol (500 ml) and added to a saturated solution of fumaric acid (16.7 g) in methanol, then the solvent was removed *in vacuo*. 35 The residue was stirred with ether (500 ml) for 3 hours and the resulting solid was

collected by filtration and dried *in vacuo* at ambient temperature for 24 hours to give 3-(benzo[*b*]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole fumarate (56.8 g) as a white solid, m.p. 161 – 162 °C.

5    Example 36

In a manner similar to that described in Example 35, 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde was reacted with ethyltriphenylphosphonium bromide and *n*-butyllithium to give crude product which was purified by flash chromatography over silica using a 19:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents removed *in vacuo* to give a 3.7:1 mixture of *E*- and *Z*-3-(benzo[*b*]thiophen-3-yl)-2-prop-1-enyl-5,6-dihydroimidazo[2,1-*b*]thiazole as a yellow solid, m.p. 62 – 68 C.

15    Example 37

In a manner similar to that described in Example 6, 3-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (prepared in a manner similar to that described in WO 97/02269) was brominated, then reacted with ethylmagnesium chloride followed by dimethylformamide to give 3-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carboxaldehyde. This was reduced with sodium borohydride in a manner similar to that described in Example 2 to give [3-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-2-yl]methanol as an off-white solid; m.p. 174 – 176 °C.

25    Example 38

A mixture of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.5 g; prepared in a manner similar to that described in Example 6), hydroxylamine hydrochloride (0.16 g) and formic acid (1.3 ml) was heated at 90 – 95 °C for 25 hours, then diluted with ether (50 ml). The resulting solid was collected by filtration, washed with ether (30 ml) and purified by flash chromatography over silica

using 95:5 followed by 85:15 mixtures of dichloromethane and methanol as eluants. Appropriate fractions were combined, and the solvents were removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carbonitrile 0.3 formate (0.12 g) as a white solid, m.p. 195 – 196 °C.

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Example 39

A solution of diethyl benzylphosphonate (1.5 ml) in tetrahydrofuran (10 ml) was added dropwise at ambient temperature under nitrogen to a stirred suspension of sodium hydride (60% dispersal in mineral oil; 0.26 g) in tetrahydrofuran (15 ml), 10 then the mixture was stirred at ambient temperature for 20 minutes. 3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.83 g; prepared in a manner similar to that described in Example 6) was added in one portion, the mixture was stirred at ambient temperature for 72 hours, then it was quenched by the addition of water (30 ml). The product was extracted into 15 dichloromethane (3 x 30 ml), the combined extracts were dried ( $MgSO_4$ ), and the solvents were removed *in vacuo*. The residue was triturated with ether (20 ml) and the resulting solid was collected by filtration. The ethereal liquors were concentrated *in vacuo* and the residue was triturated with ether (10 ml) to give a second crop of solid. The combined solids were dried *in vacuo* to give 3-(benzo[*b*]thiophen-3-yl)-2- 20 styryl-5,6-dihydroimidazo[2,1-*b*]thiazole (0.49 g) as a yellow solid, m.p. 153 – 155 °C.

Example 40

In a manner similar to that described in Example 6, 3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (prepared by basification of 25 the hydrobromide salt obtained in a manner similar to that described in WO 97/02269) was brominated, then reacted with ethylmagnesium chloride followed by dimethylformamide to give 3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a yellow solid, m.p. 258 – 260 °C,

Example 41

Sodium borohydride (0.06 g) was added to a stirred suspension of 3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.31 g) in ethanol (15 ml), the mixture was stirred at ambient temperature for 4 hours, then water (15 ml) was added. The resulting solid was collected by filtration, washed with ether (15 ml) and dried *in vacuo* at 60 °C to give [3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (0.14 g) as a white solid, m.p. 204 – 206 °C.

10   Example 42

[3-(5-Chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-methanol (0.6 g) was prepared in a manner similar to that described in Examples 40 and 41. However, on this occasion the product was impure. Consequently it was purified by preparative-scale hplc using mixtures of acetonitrile and aqueous triethylammonium formate buffer as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo*. The residue was triturated with water (2 x 3 ml) and the resulting solid was collected by filtration and dried *in vacuo* at 60 °C to give [3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-methanol formate (0.19 g) as an off-white solid, m.p. 171 – 173 °C.

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Example 43

In a manner similar to that described in Example 23, 3-(benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (5 g) was reacted with ethylmagnesium chloride followed by diphenyl disulphide to give 25 3-(benzo[*b*]thiophen-3-yl)-2-(phenylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole (0.6 g) as a yellow solid, m.p. 123 – 125 °C.

Example 44

Methylamine (2M solution in tetrahydrofuran; 8.7 ml) and sodium triacetoxyborohydride (0.56 g) were added under nitrogen to a stirred solution of 3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.5 g; prepared in a manner similar to that described in Example 6) in tetrahydrofuran (20 ml), then the mixture was stirred at ambient temperature for 72 hours. Further methylamine solution (4.3 ml) was added, the mixture was stirred at ambient temperature for 48 hours, then it was quenched by the addition of saturated aqueous sodium hydrogencarbonate solution (50 ml). The product was extracted into ethyl acetate (3 x 30 ml), the combined extracts were washed with water (30 ml) and saturated aqueous sodium chloride solution (30 ml), then they were dried ( $\text{MgSO}_4$ ) and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 9:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to give [3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-*N*-methylmethylamine (0.19 g) as a waxy solid, m.p. 102 – 104 °C.

Example 45

A solution of oxalyl chloride (13 ml) in dichloromethane (20 ml) was added dropwise at –10 – 0 °C under nitrogen to a stirred solution of cyclopropylacetic acid (5 g) and dimethylformamide (2 drops) in dichloromethane (20 ml), then the mixture was stirred at ambient temperature for 24 hours and the solvent was removed *in vacuo* to leave cyclopropylacetyl chloride as a brown oil which was used without purification.

Potassium carbonate (9.2 g) was added in portions at 0 – 5 °C over 10 minutes to a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (5.1 g) in the minimum volume of water, then dichloromethane (30 ml) was added. The above cyclopropylacetyl chloride was dissolved in dichloromethane (20 ml) and the solution was added dropwise at –5 – 0 °C to the dimethylhydroxylamine solution. The mixture was stirred at 0 °C for 30 minutes and at ambient temperature for 2 hours, then the product was extracted into dichloromethane (3 x 50 ml). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed *in vacuo* to give

cyclopropyl-N-methoxy-N-methylacetamide (6.2 g) as a pale brown oil which was used without purification.

A few drops of a solution of 3-bromobenzo[*b*]thiophene (8.7 g) in tetrahydrofuran (35 ml) were added under nitrogen to a mixture of magnesium turnings (1.05 g), 2 crystals of iodine and tetrahydrofuran (5 ml), and the mixture was warmed gently to initiate the reaction. The remainder of the solution was then added at a rate sufficient to maintain gentle reflux. When the addition was complete, the mixture was stirred at reflux temperature for 1.5 hours then allowed to cool to ambient temperature. A solution of cyclopropyl-N-methoxy-N-methylacetamide (6 g) in tetrahydrofuran (35 ml) was added at ambient temperature, the mixture was stirred at reflux temperature for 5 hours, and allowed to stand at ambient temperature for 18 hours, then it was quenched by the addition of 2M hydrochloric acid (50 ml) and stirred at ambient temperature for 1 hour. The product was extracted into ethyl acetate (2 x 100 ml), the combined extracts were washed with water (2 x 30 ml) and saturated aqueous sodium chloride solution (2 x 30 ml), then they were dried ( $MgSO_4$ ) and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 1:3 mixture of dichloromethane and petroleum ether (b.p. 60 – 80 °C) as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to give 1-(benzo[*b*]thiophen-3-yl)-2-cyclopropylethan-1-one (4.15 g) as an orange oil which was used without further purification.

Phenyltrimethylammonium tribromide (1.74 g) was added under nitrogen to a stirred solution of 1-(benzo[*b*]thiophen-3-yl)-2-cyclopropylethan-1-one (1 g) in tetrahydrofuran (15 ml), the mixture was stirred at ambient temperature for 18 hours, then it was filtered and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (12 ml), 2-imidazolidinethione (0.47 g) and acetic acid (4 ml) were added, the mixture was heated under reflux under nitrogen for 18 hours, then the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 1:3 mixture of dichloromethane and ether as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 3-(benzo[*b*]thiophen-3-yl)-2-cyclopropyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (0.72 g) as an off-white solid, m.p. 181 – 183 °C.

Example 46

A solution of iodine monochloride (1.83 g) in dichloromethane (5 ml) was added dropwise at ambient temperature to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (3.8 g; prepared in a manner similar to that described in Example 6) in dichloromethane (200 ml) and the mixture was stirred at ambient temperature for 15 minutes. The resulting solid was collected by filtration, washed with dichloromethane (50 ml) and dried in air to give 3-(benzo[*b*]thiophen-3-yl)-2-iodo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride (1.3 g) as a pale yellow solid, m.p. 194.7 – 195.2 °C.

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Example 47

A solution of dimethyl 2-oxopropylphosphonate (1.28 g) in tetrahydrofuran (10 ml) was added dropwise at ambient temperature under nitrogen to a stirred suspension of sodium hydride (60% dispersion in mineral oil; 0.46 g) in tetrahydrofuran (15 ml), then the mixture was stirred at ambient temperature for 20 minutes. 3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carbox-aldehyde (2 g; prepared in a manner similar to that described in Example 6) was added in portions, the mixture was stirred at ambient temperature for 18 hours and at reflux temperature for 7 hours, then it was allowed to stand at ambient temperature for 18 hours. The solvent was removed *in vacuo*, the residue was diluted with water (200 ml), and the product was extracted into dichloromethane (200 ml). The extract was dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was removed *in vacuo*; then the residue was purified by flash chromatography over silica using a 19:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to give 4-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-ene-2-one (1.15 g) as a yellow solid, m.p. 164 – 166 °C.

Sodium borohydride (36 mg) was added to a stirred solution of 4-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-ene-2-one (0.28 g) in ethanol (10 ml), the mixture was stirred at ambient temperature for 3 hours, then the solvent was removed *in vacuo*. The residue was diluted with water (100 ml) and the product was extracted into dichloromethane (100 ml), then the extract was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed *in vacuo*. The residue was triturated with ether (20 ml) and the resulting solid was collected by filtration and

dried *in vacuo* to give 4-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-en-2-ol (0.16 g) as an off-white solid, m.p. 161 – 162 °C.

Example 48

5 In a manner similar to that described in Example 17, 3-(benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide was reacted with ethylmagnesium chloride followed by 3-bromo-2-methylpropene and fumaric acid to give 3-(benzo[*b*]thiophen-3-yl)-2-(2-methylprop-2-enyl)-5,6-dihydroimidazo[2,1-*b*]-thiazole fumarate as an off-white solid, m.p. 54 – 64 °C.

10

Example 49

A solution of tetraethyl (dimethylamino)methylenediphosphonate (2.32 g) in 1,4-dioxane (5 ml) was added dropwise at ambient temperature under nitrogen to a stirred suspension of sodium hydride (60% dispersion in mineral oil; 0.28 g) in 1,4-dioxane (5 ml), and the mixture was stirred at ambient temperature until the evolution of hydrogen ceased. 3-(Benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (2 g; prepared in a manner similar to that described in Example 6) was added, the mixture was stirred at 60 °C for 1.3 hours and at ambient temperature for 18 hours, then it was poured into water (50 ml). The product was extracted into ethyl acetate (3 x 30 ml), the combined extracts were dried ( $MgSO_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 93:7 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to give diethyl 2-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-(dimethylamino)ethenylphosphonate (1.78 g) as a red oil which was used without further purification.

A mixture of 2-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-(dimethylamino)ethenylphosphonate (1.7 g) and concentrated hydrochloric acid (12 ml) was heated under reflux for 1 hour then cooled in ice. The product was extracted into dichloromethane (3 x 30 ml), the combined extracts were dried ( $MgSO_4$ ) and the solvent was removed *in vacuo*. The residue was dissolved in water

(30 ml), the solution was neutralised by the addition of an excess of saturated aqueous sodium hydrogencarbonate solution, and the product was extracted into dichloromethane (3 x 30 ml). The combined extracts were dried ( $\text{MgSO}_4$ ) and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (2 ml), oxalic acid (15 mg) was added, and the solvent was removed *in vacuo*. The residue was triturated with ether (10 ml) and the resulting solid was collected by filtration and dried *in vacuo* to give ethyl [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]acetate oxalate (40 mg) as an off-white solid, m.p. 102 – 104 °C.

10 Example 50

sec-Butyllithium (1.25M solution in a 92:8 mixture of cyclohexane and hexane; 100 ml) was added dropwise at –70 °C under nitrogen to a stirred solution of 4-fluorophenyl methyl sulphide (22.0 g) in tetrahydrofuran, then the mixture was stirred at –70 °C for 65 minutes. Dimethylformamide (13.2 ml) was added dropwise at –68 °C to -70 °C, the stirred mixture was allowed to warm to ambient temperature slowly over 20 hours, then it was added to a solution of acetic acid (10 ml) in water (500 ml). The product was extracted into ether (3 x 150 ml), then the combined extracts were washed with 2M hydrochloric acid (200 ml) and saturated aqueous sodium chloride solution (200 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue (25 g), which was used without further purification, was estimated to consist predominantly of a 2:3 mixture of 4-fluorophenyl methyl sulphide and 2-fluoro-5-(methylthio)benzaldehyde respectively by nuclear magnetic resonance spectroscopy.

25 A stirred mixture of methyl thioglycolate (8.9 ml), crude 2-fluoro-5-(methylthio)benzaldehyde (25 g), dimethyl acetamide (250 ml) and *N,N*-diisopropylethylamine (42 ml) was heated at 140 – 150 °C under nitrogen for 3.5 hours, then the solvent was removed *in vacuo*. Water (650 ml) was added to the residue, then the product was extracted into dichloromethane (3 x 150 ml). The combined extracts were washed with water (3 x 150 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed *in vacuo*. The residue was purified by trituration with ether (250 ml), then the resulting solid was collected by filtration, washed with ether (2 x 50 ml), and dried *in vacuo* to give methyl 5-(methylthio)benzo[*b*]thiophene-2-carboxylate (13.3 g) as a pale yellow solid, m.p. 89.7 – 90.4 °C.

Sodium hydroxide (8 g) was dissolved in water (100 ml) then the solution was added to a stirred solution of methyl 5-(methylthio)benzo[b]thiophene-2-carboxylate (23.8 g; prepared in a manner similar to that described above) in methanol (300 ml).

5 The mixture was heated under reflux for 10 minutes then allowed to stand at ambient temperature for 3 days. The suspension was concentrated to a total volume of approximately 250 ml by heating, then water (100 ml) was added and the mixture hot filtered to remove insoluble material. A solution of concentrated hydrochloric acid (40 ml) in water (20 ml) was added to the filtrate and the resulting solid was collected  
10 by filtration and washed with water, then dried *in vacuo* at 80 °C to give 5-(methylthio)benzo[b]thiophene-2-carboxylic acid (21 g) as a pale yellow solid, m.p. 186 – 186.5 °C.

A mixture of copper powder (5.3 g), 5-(methylthio)benzo[b]thiophene-2-carboxylic acid (20 g) and quinoline (100 ml) was stirred and heated under reflux under nitrogen for 30 minutes, then hot filtered. The filtrate was added to a mixture of concentrated hydrochloric acid (100 ml), ice (500 g) and ether (200 ml), then the resulting solid was collected by filtration and washed with ether (200 ml). The aqueous phase was separated and further product extracted from it into ether (2 x 150 ml). The combined ethereal solutions were washed with 2M hydrochloric acid (200 ml) and water (200 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed *in vacuo* to give 5-(methylthio)benzo[b]thiophene (14.7 g) as a light brown solid which was used without further purification.

25 A solution of 5-(methylthio)benzo[b]thiophene (14.7 g) in dichloromethane (180 ml) was added at <0 °C under nitrogen to a stirred mixture of aluminium bromide (26.2 g), bromoacetyl bromide (7.12 ml) and dichloromethane (120 ml), the resulting dark red-brown solution was stirred at <0 °C for 30 minutes and at ambient temperature for 20 hours, then it was added to a mixture of ice (600 g) and concentrated hydrochloric acid (50 ml). Dichloromethane (300 ml) was added and insoluble materials were removed by filtration (Celite ®). The aqueous phase was separated and further product extracted from it into dichloromethane (300 ml), then the combined dichloromethane solutions were dried ( $\text{MgSO}_4$ ), and the solvent was removed *in vacuo*. The residue was dissolved in a mixture of acetic acid (200 ml) and dichloromethane (200 ml), a solution of 2-imidazolidinethione (5.29 g) in acetic acid (200 ml) was added, then the dichloromethane was removed by distillation. The  
30  
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remaining mixture was heated under reflux for two hours, then the total volume was reduced to approximately 200 ml by heating *in vacuo*. The hot solution was removed from insoluble material by decantation, then allowed to cool. Further solid precipitated and was removed as before, then the solvents were removed *in vacuo*

5 at 50 °C. The residue was mixed with water (300 ml) and 5M aqueous sodium hydroxide solution (300 ml) then the product was extracted into dichloromethane (300 ml). The extract was dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was removed *in vacuo*. The residue was partially purified by flash chromatography over silica using ethyl acetate then an 8:1:1 mixture of ethyl acetate, methanol and triethylamine as

10 eluants. Appropriate fractions were combined and the solvents removed *in vacuo* to leave 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole as a yellow-brown gum (3.6 g), which was used without further purification.

A solution of bromine (1.87 g) in dichloromethane (10 ml) was added

15 dropwise at 15 – 20 °C to a stirred solution of 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole (3.55 g) in dichloromethane (80 ml), the mixture was stirred at ambient temperature for 10 minutes, then the dichloromethane solution was separated by decantation from insoluble materials and concentrated *in vacuo*. The residue was triturated with dichloromethane (10 ml) and the resulting

20 solid was collected by filtration and dried *in vacuo* to give 2-bromo-3-[5-(methylthio)-benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (2.97 g) as a yellow-brown solid, m.p. 260 - 265 °C.

## 25

Example 51

Ethylmagnesium chloride (2.8M solution in tetrahydrofuran; 8.76 ml) was added at –10 °C under nitrogen to a stirred suspension of 2-bromo-3-[5-(methylthio)-benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (2.9 g) in tetrahydrofuran (40 ml), then the mixture was stirred at ambient temperature for 90

30 minutes and cooled to –5 °C. Dimethylformamide (5 ml) was added, the resulting suspension was stirred for 2 hours at ambient temperature, then ethyl acetate (200 ml) and saturated aqueous ammonium chloride solution (200 ml) were added. The ethyl acetate layer was separated, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents removed *in vacuo* to give 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]-thiazole-2-carboxaldehyde (1.4 g) as a solid, m.p. 157-158.5 °C, which was used without further purification.

Sodium borohydride (0.114 g) was added to a stirred solution of 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.664 g) in ethanol (40 ml), then the mixture was stirred at ambient temperature for 24 hours and quenched by the addition of 5M hydrochloric acid (10 ml). The mixture was basified by the addition of an excess of 1M aqueous sodium hydroxide solution and concentrated *in vacuo* to remove ethanol, then the product was extracted into dichloromethane (3 x 30 ml). The combined extracts were dried ( $\text{MgSO}_4$ ), the solvent was removed *in vacuo*, and the residue was purified by Biotage flash chromatography over silica using a 34:3:3 mixture of ethyl acetate, industrial methylated spirit and triethylamine as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo*, then the residue was triturated with ether (10 ml). The resulting solid was collected by filtration and dried in air to give {3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl}-methanol (0.13 g) as a beige solid, m.p. 164 – 167 °C.

#### Example 52

In a manner similar to that described in Example 22, [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (0.5 g) was reacted with sodium hydride and bromomethylcyclopropane followed by fumaric acid. In this case the salt formation was carried out in methanol solution and no solid product precipitated. Consequently, the solvent was removed *in vacuo* and the residue was triturated with ether (10 ml). The resulting solid was collected by filtration and dried *in vacuo* to give 3-(benzo[*b*]thiophen-3-yl)-2-cyclopropylmethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole fumarate (40 mg) as a pale brown solid, m.p. 82 – 98 °C.

#### Example 53

Sodium hydride (60% dispersion in mineral oil; 0.153 g) was added in portions at ambient temperature over 10 minutes to a stirred suspension of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (1 g) in dimethylformamide (50 ml), then the mixture was stirred at ambient temperature for 2 hours. 1-Chloroprop-2-yne (276  $\mu\text{l}$ ) was added, and stirring at ambient temperature was continued for a further 2 hours. Further 1-chloroprop-2-yne (27  $\mu\text{l}$ ) was added and the mixture was stirred at ambient temperature for 18 hours. Water (50 ml) was

added, the product was extracted into ethyl acetate (3 x 50 ml), then the combined extracts were washed with water (4 x 25 ml) and saturated aqueous sodium chloride solution (25 ml), dried ( $\text{MgSO}_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using 5 - 8% mixtures of 5 methanol in dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo*. The residue was dissolved in methanol (15 ml), fumaric acid (0.185 g) was added, the mixture was stirred at ambient temperature for 5 hours, then it was warmed to dissolve the product and filtered to remove a small amount of insoluble material. The solvent was removed *in vacuo* to 10 give 3-(benzo[*b*]thiophen-3-yl)-2-prop-2-ynylloxymethyl-5,6-dihydroimidazo[2,1-*b*]-thiazole fumarate (0.67 g) as a brown solid, m.p. 120 °C (softens 80 – 90 °C).

Example 54

15 A solution of potassium hydroxide (4.87 g) in a mixture of ethanol (140 ml) and water (35 ml) was added in one portion at ambient temperature under nitrogen to a stirred solution of 2-methoxybenzenethiol (10.6 ml) in a mixture of ethanol (125 ml) and water (7.5 ml), then the mixture was stirred at ambient temperature for 3.5 hours. A solution of 1-chloro-4-phenoxybut-2-yne (15.7 g) in a mixture of ethanol 20 (125 ml) and water (7.5 ml) was added dropwise over 1.5 hours, then the mixture was stirred at ambient temperature for 18 hours, and the solvents were removed *in vacuo*. The residue was diluted with water (75 ml), the product was extracted into ethyl acetate (2 x 115 ml), then the combined extracts were washed with water (50 ml) and saturated aqueous sodium chloride solution (50 ml), dried ( $\text{MgSO}_4$ ), and the 25 solvent was removed *in vacuo* to leave 1-(2-methoxyphenylthio)-4-phenoxybut-2-yne (24.7 g) as a yellow oil which was used without further purification.

A solution of 3-chloroperoxybenzoic acid (70% purity; 9.1 g) in chloroform (210 ml) was added dropwise at 0 – 5 °C over 1.5 hours to a stirred solution of 30 1-(2-methoxyphenylthio)-4-phenoxybut-2-yne (10.5 g) in chloroform (95 ml), the mixture was stirred at ambient temperature for 18 hours, then it was washed with 5% aqueous sodium carbonate solution (3 x 120 ml) and water (3 x 80 ml) and dried ( $\text{MgSO}_4$ ). The chloroform solution was stirred and heated under reflux for 7 hours and allowed to stand at ambient temperature for 18 hours, then it was washed with 35 5M aqueous sodium hydroxide solution (115 ml), water (4 x 110 ml) and saturated aqueous sodium chloride solution (100 ml) and dried ( $\text{MgSO}_4$ ). The solvent was

removed *in vacuo* to leave 1-(7-methoxy-2,3-dihydrobenzo[*b*]thiophen-3-yl)-2-phenoxyethan-1-one (10.7 g) as a brown gum which was used without further purification.

5 A mixture of 1-(7-methoxy-2,3-dihydrobenzo[*b*]thiophen-3-yl)-2-phenoxyethan-1-one (10.7 g), acetic acid (100 ml) and concentrated sulphuric acid (12 drops) was heated at 90 – 95 °C for 3 hours then cooled to ambient temperature and poured onto water (800 ml). The product was extracted into dichloromethane (2 x 250 ml), the combined extracts were washed with 2M aqueous sodium hydroxide 10 solution (2 x 200 ml) and water (3 x 200 ml), then they were dried ( $\text{MgSO}_4$ ) and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 1:1 mixture of dichloromethane and petroleum ether (b.p. 60 – 80 °C) as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to give 1-(7-methoxybenzo[*b*]thiophen-3-yl)ethan-1-one (2 g) as a brown oil 15 which was used without further purification.

Phenyltrimethylammonium tribromide (2.55 g) was added in portions at ambient temperature under nitrogen over 20 minutes to a stirred solution of 1-(7-methoxybenzo[*b*]thiophen-3-yl)ethan-1-one (1.4 g) in tetrahydrofuran (40 ml), 20 the mixture was stirred at ambient temperature for 1 hour, then it was filtered and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (30 ml), 2-imidazolidinethione (0.69 g) and acetic acid (20 ml) were added, the mixture was heated under reflux for 18 hours, then it was cooled to ambient temperature. The resulting solid was collected by filtration, washed with ether (20 ml) and dried *in 25 vacuo* at 60 °C to give 3-(7-methoxybenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (1.48 g) as a grey solid, m.p. 277 – 279 °C.

3-(7-Methoxybenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole 30 hydrobromide (1.48 g) was basified by the addition of 2M aqueous sodium hydroxide solution (110 ml) and the free base was extracted into dichloromethane (150 ml). The extract was washed with water (2 x 70 ml), dried ( $\text{MgSO}_4$ ), and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (23 ml), then the stirred solution was cooled to 0 - 5°C and a solution of bromine (0.68 g) in dichloromethane (4.7 ml) was added dropwise over 45 minutes. The mixture was 35 stirred at 0 – 5 °C for 30 minutes and allowed to stand at ambient temperature for 18

hours, then the resulting solid was collected by filtration, washed with dichloromethane (20 ml) and dried *in vacuo* to give 2-bromo-3-(7-methoxybenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (1.22g) as a white solid, m.p. 240 – 242 °C.

5

Example 55

Sodium hydride (60% dispersion in mineral oil; 0.38 g) was added in portions at ambient temperature over 10 minutes to a stirred suspension of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (2.5 g) in dimethylformamide (50 ml), then the mixture was stirred at ambient temperature for 2 hours. 2-Bromopropane (0.9 ml) was added and stirring at ambient temperature was continued for 2 hours. Further 2-bromopropane (0.4 ml) was added and the mixture was stirred at ambient temperature for 72 hours. Sodium hydride (60% dispersion in mineral oil; 0.07 g) was added, the mixture was stirred for 10 minutes, then 2-bromopropane (0.16 ml) was added and the mixture was stirred at ambient temperature for 18 hours. Water (100 ml) was added, the product was extracted into ethyl acetate (100 + 2 x 75 ml), then the combined extracts were washed with water (3 x 100 ml) and saturated aqueous sodium chloride solution (100 ml), dried (MgSO<sub>4</sub>); and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 1:19 mixture of methanol and dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 9:1 mixture of ethyl acetate and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to give 3-(benzo[*b*]thiophen-3-yl)-2-isopropoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole (0.12 g) as a yellow solid, m.p. 64 – 66 °C.

30

Example 56

Sodium hydride (60% dispersion in mineral oil; 0.46 g) was added in portions at ambient temperature over 10 minutes to a stirred suspension of [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol (3 g) in dimethylformamide (80 ml), then the mixture was stirred at ambient temperature for 2 hours. Bromomethylcyclobutane (1.7 g) was added dropwise and the mixture was stirred at ambient temperature for 2.5 hours. Further bromomethylcyclobutane (0.16 g) was

added dropwise and the mixture was stirred at ambient temperature for 1 hour. Further bromomethylcyclobutane (0.16 g) was added dropwise and the mixture was stirred at ambient temperature for 18 hours. Tlc showed starting material still remained, so bromomethylcyclobutane (0.32 g) was added and the mixture was 5 stirred at ambient temperature for 2 hours and at 55 °C for 1 hour. Further sodium hydride (0.042 g) and bromomethylcyclobutane (0.8 g) were added and the mixture was stirred at 55 °C for 1 hour and at ambient temperature for 18 hours. Water (100 ml) was added, the product was extracted into ethyl acetate (100 + 3 x 75 ml), then the combined extracts were washed with water (4 x 75 ml) and saturated 10 aqueous sodium chloride solution (75 ml), dried ( $MgSO_4$ ), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 1:19 mixture of methanol and dichloromethane as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 3:1 mixture of petroleum ether 15 (b.p. 60 – 80 °C) and ethyl acetate followed by a 19:1 mixture of dichloromethane and methanol as eluants. Appropriate fractions were combined and the solvents were removed *in vacuo*. A sample (30 mg from 70mg) of the residue was further purified by preparative scale hplc on a C8 symmetry shield column using a 2:3 mixture of acetonitrile and triethylammonium formate buffer as eluant. Appropriate 20 fractions were combined and the solvents removed *in vacuo* to give 3-(benzo[*b*]thiophen-3-yl)-2-cyclobutylmethoxymethyl-5,6-dihydroimidazo[2,1-*b*]-thiazole (12 mg) as a brown gum,  $^1H$ -nmr ( $DMSO-d_6$ ):  $\delta_H$  1.61 – 1.84 (6H, m, 3 x cyclobutane  $CH_2$ ), 2.36 – 2.41 (1H, m, cyclobutane  $CH$ ), 3.22 (2H, d,  $CH_2O$ ), 3.49 – 3.61 (2H, m,  $CH_2N$ ), 3.98 – 4.05 (2H, m,  $CH_2\bar{O}$ ); 4.11 – 4.15 (2H, m,  $CH_2N$ ), 7.45 – 25 7.49 (2H, m, 2 x ArH), 7.77 – 7.81 (1H, m, ArH), 8.01 (1H, s, ArH), 8.08 – 8.11 (1H, m, ArH).

#### Example A

30 The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled 5 into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

10 Tablets are prepared from the following ingredients.

|                         | <u>Parts by weight</u> |
|-------------------------|------------------------|
| Active compound         | 10                     |
| Lactose                 | 190                    |
| Maize starch            | 22                     |
| 15 Polyvinylpyrrolidone | 10                     |
| Magnesium stearate      | 3                      |

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate 20 and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

25

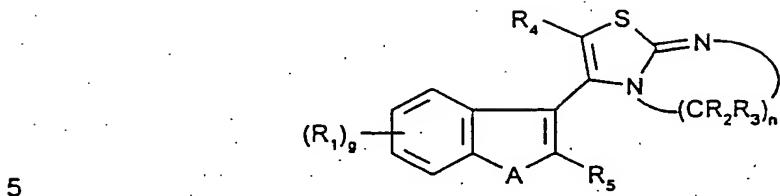
Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

30 d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of 35 active ingredient.

Claims

## 1) Compounds of Formula I



including pharmaceutically acceptable salts thereof in which

A is S or O;

10

g is 0, 1, 2, 3 or 4;

n is 2 or 3;

15 R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) 20 a hydroxyalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms; k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two 25 alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being the same or different when g is 2, 3 or 4;

R<sub>2</sub> and R<sub>3</sub> are each H;

30

R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, an α-hydroxy(2-C<sub>1-3</sub>alkoxyphenyl)methyl group, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a

hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, a hydroxycycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 8 carbon atoms, an arylalkenyl group containing 8 to 10 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a C<sub>3-7</sub>alkynylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>4-7</sub>cycloalkylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkylthioC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group, a C<sub>1-3</sub>alkylthio group, an arylthio group, a C<sub>1-6</sub> alkanoyl group, a C<sub>3-6</sub> alkoxy carbonylalkyl group, cyano, halo, a C<sub>1-4</sub>alkyliminomethyl group, a C<sub>1-4</sub>alkylaminoalkyl group or a hydroxyiminomethyl group;

10

R<sub>5</sub> is H or halo.

15

2) Compounds of Formula I according to claim 1 including pharmaceutically acceptable salts thereof in which

20

A is S or O;

g is 0, 1, 2, 3, or 4;

n is 2 or 3;

R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) a hydroxyalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxy carbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphonamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being the same or different when g is 2, 3 or 4;

35

R<sub>2</sub> and R<sub>3</sub> are each H;

R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, a hydroxycycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 8 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkylthioC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group, a C<sub>1-3</sub>alkylthio group, a C<sub>1-6</sub> alkanoyl group, halo, a C<sub>1-4</sub>alkyliminomethyl group or a hydroxyiminomethyl group; and

R<sub>5</sub> is H or halo.

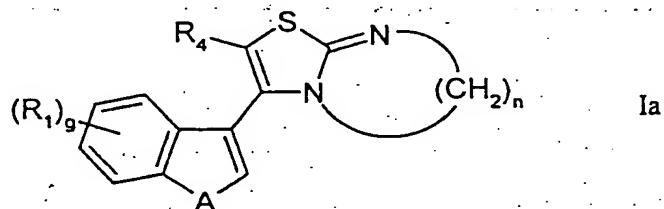
- 3) Compounds as claimed in either claim 1 or claim 2 in which A is S.
- 15 4) Compounds as claimed in either claim 1 or claim 2 in which A is O.
- 5) Compounds as claimed in any previous claim in which R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, an alkenyl group containing 2 carbon atoms optionally substituted by one or more C<sub>1-2</sub>alkyl groups, a C<sub>1-4</sub>alkyliminomethyl group or a hydroxyiminomethyl group.
- 25 6) Compounds as claimed in any previous claim in which R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 5 carbon atoms, a hydroxyalkenyl group containing 3 to 5 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond or an alkenyl group containing 2 carbon atoms optionally substituted by one or more methyl groups.
- 30 7) Compounds as claimed in any previous claim in which R<sub>4</sub> represents hydroxymethyl or vinyl.

8) Compounds as claimed in any previous claim in which n is 2.

9) Compounds as claimed in any previous claim in which g is 0 or 1, and R<sub>1</sub> is  
a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by  
one or more halo, or c) an alkoxy group containing 1 to 3 carbon atoms optionally  
substituted by one or more halo.

10) Compounds as claimed in any previous claim in which R<sub>5</sub> is H.

10 11) Compounds according to claim 1 of Formula Ia



including pharmaceutically acceptable salts thereof in which

15 A is S or O;

g is 0, 1, 2, 3 or 4;

n is 2 or 3;

20 R<sub>1</sub> is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by  
one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g)  
a hydroxalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group  
containing 1 to 6 carbon atoms, j) an alkoxy carbonyl group containing 2 to 6 carbon  
atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally  
N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a  
30 sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two  
alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally

substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R<sub>1</sub> being the same or different when g is 2, 3 or 4; and

R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 6 carbon atoms, an  $\alpha$ -hydroxy(2-C<sub>1-3</sub> alkoxyphenyl)methyl group, a hydroxyalkenyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 6 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, an alkenyl group containing 2 to 8 carbon atoms, an arylalkenyl group containing 8 to 10 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a C<sub>3-7</sub>alkynylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>4-7</sub>cycloalkylalkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxyC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkylthioC<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group, a C<sub>1-3</sub>alkylthio group, an arylthio group, a C<sub>1-6</sub>alkanoyl group, a C<sub>3-6</sub>alkoxycarbonylalkyl group, cyano, halo, a C<sub>1-4</sub>alkyliminomethyl group, a C<sub>1-4</sub>alkylaminomethyl group or a hydroxyiminomethyl group.

15           12) Compounds according to claim 11 in which A is S.

16           13) Compounds according to claim 11 or claim 12 in which n is 2.

20           14) Compounds according to any one of claims 11 to 13 in which g is 0 or 1.

25           15) Compounds according to any one of claims 11 to 14 in which R<sub>1</sub> is halo, an alkoxy group containing 1 to 3 carbon atoms, or an alkylthio group containing 1 to 3 carbon atoms.

17           16) Compounds according to any one of claims 11 to 15 in which A is O.

30           18) Compounds according to any one of claims 11 to 16 in which R<sub>4</sub> represents a hydroxyalkyl group containing 1 to 4 carbon atoms, an  $\alpha$ -hydroxy(2-C<sub>1-3</sub> alkoxyphenyl)methyl group, a hydroxyalkenyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the double bond, a hydroxyalkynyl group containing 3 to 4 carbon atoms in which hydroxy is not attached directly to either carbon of the triple bond, an alkenyl group containing 2 to 3 carbon atoms, a C<sub>1-3</sub>alkylthio group, a C<sub>1-2</sub>alkanoyl group or a hydroxyiminomethyl group.

18) A compound selected from  
5      3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde;  
[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;  
10     3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde  
oxime;  
15     1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]ethanol;  
3-(benzo[b]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole;  
20     3-(benzo[b]thiophen-3-yl)-2-bromo-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-methylethanol;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]propan-1-ol;  
25     2-bromo-3-(5-methoxybenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
2-bromo-3-(5-chlorobenzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
30     3-(benzo[b]thiophen-3-yl)-2-ethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-en-1-ol;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-2-yn-1-ol;  
35     3-(benzo[b]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole;  
2-allyl-3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
40     [3-(benzo[b]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;  
N-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methylidene]-1-  
methylethylamine;  
45     3-(benzo[b]thiophen-3-yl)-2-chloro-5,6-dihydroimidazo[2,1-*b*]thiazole;  
2-acetyl-3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
3-(benzo[b]thiophen-3-yl)-2-(methoxymethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
3-(benzo[b]thiophen-3-yl)-2-(methylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
50     3-(benzo[b]thiophen-3-yl)-2-(1-methylvinyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylpropan-1-  
ol;  
1-[3-(benzo[b]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]butan-1-ol;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylbut-3-en-1-ol;

5 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-3-methylbutan-1-ol;

10 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pentan-1-ol;

15 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-yn-1-ol;

20 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-en-1-ol;

25 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylprop-2-en-1-ol;

30 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pent-4-en-1-ol;

35 [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl](2-methoxyphenyl)methanol;

40 3-(benzo[*b*]thiophen-3-yl)-2-prop-1-enyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

45 [3-(benzo[*b*]thiophen-3-yl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-2-yl]methanol;

50 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carbonitrile;

55 3-(benzo[*b*]thiophen-3-yl)-2-styryl-5,6-dihydroimidazo[2,1-*b*]thiazole;

60 3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde;

65 [3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;

70 3-(benzo[*b*]thiophen-3-yl)-2-(phenylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole;

75 [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-*N*-methylmethylamine;

80 3-(benzo[*b*]thiophen-3-yl)-2-cyclopropyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

85 3-(benzo[*b*]thiophen-3-yl)-2-iodo-5,6-dihydroimidazo[2,1-*b*]thiazole;

90 4-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-en-2-ol;

95 3-(benzo[*b*]thiophen-3-yl)-2-(2-methylprop-2-enyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

100 ethyl [3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]acetate;

105 2-bromo-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole;

110 {3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl}methanol;

3-(benzo[*b*]thiophen-3-yl)-2-cyclopropylmethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

5      3-(benzo[*b*]thiophen-3-yl)-2-prop-2-nyloxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

2-bromo-3-(7-methoxybenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

10     3-(benzo[*b*]thiophen-3-yl)-2-isopropoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole; and

15     3-(benzo[*b*]thiophen-3-yl)-2-cyclobutylmethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole

including pharmaceutically acceptable salts thereof and individual enantiomers, racemates or other mixtures of enantiomers.

19) A compound selected from

3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde;

[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;

20     3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde oxime;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]ethanol;

25     3-(benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(benzo[*b*]thiophen-3-yl)-2-bromo-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine;

30     1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-methylethanol;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]propan-1-ol;

2-bromo-3-(5-methoxybenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

35     2-bromo-3-(5-chlorobenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(benzo[*b*]thiophen-3-yl)-2-ethoxymethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

40     1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-en-1-ol;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-2-yn-1-ol;

3-(benzo[*b*]thiophen-3-yl)-2-vinyl-5,6-dihydroimidazo[2,1-*b*]thiazole;

45     2-allyl-3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

[3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]methanol;

50     *N*-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-ylmethylidene]-1-methylethylamine;

3-(benzo[*b*]thiophen-3-yl)-2-chloro-5,6-dihydroimidazo[2,1-*b*]thiazole;

2-acetyl-3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

5 3-(benzo[*b*]thiophen-3-yl)-2-(methoxymethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(benzo[*b*]thiophen-3-yl)-2-(methylthio)-5,6-dihydroimidazo[2,1-*b*]thiazole;

10 3-(benzo[*b*]thiophen-3-yl)-2-(1-methylvinyl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylpropan-1-ol ;

15 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]butan-1-ol ;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylbut-3-en-1-ol ;

20 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-3-methylbutan-1-ol;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pentan-1-ol;

25 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]prop-2-yn-1-ol ;

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]but-3-en-1-ol ;

30 1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-2-methylprop-2-en-1-ol; and

1-[3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]pent-4-en-1-ol;

35 and pharmaceutically acceptable salts thereof.

20) A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, as claimed in any previous claim, together with a pharmaceutically acceptable diluent or carrier.

40

21) A compound of Formula I, as claimed in any previous claim, for use as a medicament.

45 22) A compound of Formula I, as claimed in any previous claim for use in the treatment of depression, anxiety, psychoses, schizophrenia, tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias,

eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, and as an aid to smoking cessation.

- 5      23) A compound of Formula I, as claimed in any previous claim for use in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage.
- 10     24) Use of a compound of Formula I, as claimed in any of claims 1 to 19, in the manufacture of a medicament for use in the treatment of depression, anxiety, psychoses, schizophrenia, tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, and as an aid to smoking cessation and in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage.
- 15     25) A method of treating depression, anxiety, psychoses, schizophrenia, tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, and seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage comprising the administration of a therapeutically effective amount of a compound of Formula I, as claimed in any of claims 1 to 19, to a patient in need thereof.
- 20     26) A method of reducing the craving to smoke in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I, as claimed in any of claims 1 to 19, to a patient in need thereof,
- 25

27) A method of reducing weight gain after smoking cessation in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I, as claimed in any of claims 1 to 19, to a patient in need thereof.

5

28) A compound of Formula I, as claimed in any of claims 1 to 19, for use in the treatment or prevention of metabolic diseases and conditions arising therefrom, in particular non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence, hyperactivity disorders, hiatal hernia and reflux esophagitis, pain, especially neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

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29) A compound of Formula I, as claimed in any of claims 1 to 19, for use in the prevention of cardiovascular disease, in reducing platelet adhesiveness, in aiding weight loss after pregnancy or in aiding weight loss after smoking cessation.

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30) The use of a compound which is a 5-HT<sub>1A</sub> agonist and which is also monoamine reuptake inhibitor particularly a noradrenaline reuptake inhibitor in the treatment of obesity and related co-morbid conditions without causing cardiovascular side effects.

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31) A method of treating obesity without causing cardiovascular side-effects comprising the administration of a compound which is a 5-HT<sub>1A</sub> agonist and which is also a monoamine reuptake inhibitor particularly a noradrenaline reuptake inhibitor to a patient in need thereof.

25

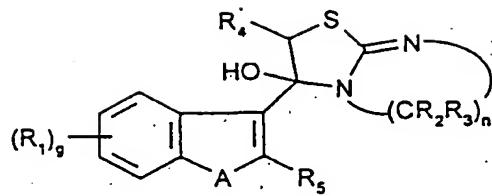
32) A compound of Formula I as claimed in any one of claims 1 to 19 for use in the treatment obesity and related co-morbid conditions.

30

33) A process for the preparation of compounds of Formula I comprising:

a) dehydrating a compound of Formula II

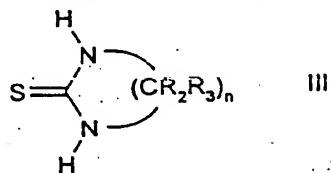
87



in which A,R<sub>1</sub>,R<sub>2</sub>,R<sub>3</sub>,R<sub>4</sub>,R<sub>5</sub>, g and n are as hereinbefore defined, optionally in the presence of an acid at a temperature in the range 0-200°C; or

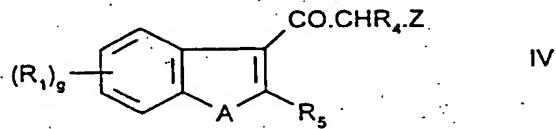
5

b) by reacting a compound of Formula III



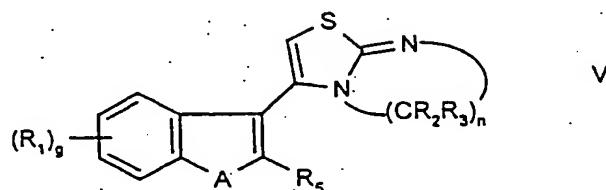
in which R<sub>2</sub>,R<sub>3</sub> and n are as hereinbefore defined, with a compound of Formula IV

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in which Z is a leaving group and A,R<sub>1</sub>,R<sub>4</sub>,R<sub>5</sub> and g are as hereinbefore defined, at a temperature in the range 0-200°C, optionally in the presence of an acid, and optionally in the presence of a solvent, without isolation of the intermediate of  
15 Formula II; or

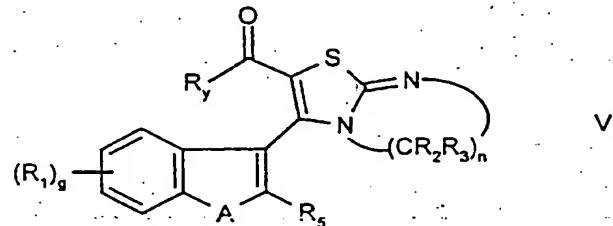
c) reacting a compound of Formula V



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in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined, with a halogenating agent at a temperature in the range -50-200°C optionally in the presence of a solvent to give compounds of Formula I in which R<sub>4</sub> represents halo; or

5 d) reacting a compound of Formula VI



in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as hereinbefore defined and Ry is H with an organometallic reagent of formula R<sub>x</sub>MgX or R<sub>x</sub>Li in which R<sub>x</sub> is a C<sub>1-5</sub> alkyl group, an alkenyl group containing 2-5 carbon atoms, an alkynyl group containing 2-5 carbon atoms or (2-C<sub>1-3</sub>alkoxyphenyl) and X is halo, in the presence of a solvent, at a temperature in the range of -50°C to the boiling point of the solvent used to give compounds of Formula I in which R<sub>4</sub> represents a group of Formula -CH(OH)R<sub>x</sub> in which R<sub>x</sub> is as hereinbefore defined; or

15 e) reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and Ry is a C<sub>1-5</sub> alkyl group, an alkenyl group containing 2-5 carbon atoms, an alkynyl group containing 2-5 carbon atoms or (2-C<sub>1-3</sub>alkoxyphenyl) with a reducing agent in the presence of a solvent, at a temperature in the range of 0°C to the boiling point of the solvent used to give compounds of Formula I in which R<sub>4</sub> represents a group of Formula -CH(OH)R<sub>y</sub> in which R<sub>y</sub> is a C<sub>1-5</sub> alkyl group, an alkenyl group containing 2-5 carbon atoms, an alkynyl group containing 2-5 carbon atoms or (2-C<sub>1-3</sub>alkoxyphenyl); or

20 f) reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and Ry is H with a reducing agent, in a solvent, at a temperature in the range of -50°C to the boiling point of the solvent used to give compounds of Formula I in which R<sub>4</sub> is hydroxymethyl; or

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g) reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> is H with hydroxylamine or a salt thereof optionally in the presence of a solvent, at a temperature in the range of 0-250°C to give compounds of Formula I in which R<sub>4</sub> is hydroxyiminomethyl; or

5 h) reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> is H with hydroxylamine or a salt thereof in the presence of formic acid at a temperature in the range of 0-250°C to give compounds of Formula I in which R<sub>4</sub> is cyano; or

10 i) reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> is H with an amine of Formula R<sub>a</sub>NH<sub>2</sub> wherein R<sub>a</sub> represents a C<sub>1-4</sub> alkyl group optionally in the presence of a solvent, optionally in the presence of an acid catalyst, at a temperature in the range 0-250°C to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkyliminomethylene group; or

15 j) reacting a compound of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkyliminomethylene group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g, and n are as hereinbefore defined, with a reducing agent in the presence of a solvent, at a temperature in the range of 0°C to the boiling point of the solvent used to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkylaminomethylene group; or

20 k) reacting a compound of Formula VI in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, g and n are as hereinbefore defined and R<sub>y</sub> represents hydrogen with an amine of formula R<sub>a</sub>NH<sub>2</sub> wherein R<sub>a</sub> represents a C<sub>1-4</sub> alkyl group and a reducing agent, in the presence of a solvent, at a temperature in the range 0°C to the boiling point of the solvent used to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-4</sub>alkylaminomethylene group; or

25 l) reacting a compound of Formula VI in which R<sub>y</sub> is a C<sub>1-5</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with an organometallic reagent of formula R<sub>x</sub>MgX or R<sub>x</sub>Li in which R<sub>x</sub> is a C<sub>1-5</sub> alkyl group and X is halo, in the presence of a solvent, at a temperature in the range of -50°C to the boiling point of the solvent

used to give compounds of Formula I in which  $R_4$  represents a group of formula  $-C(OH)R_xR_y$  in which  $R_x$  and  $R_y$  are each independently a  $C_{1-5}$  alkyl group; or

5 m) reacting a compound of Formula VI, as hereinbefore defined except that  $R_y$  is  $OR_z$  in which  $R_z$  is a  $C_{1-6}$  alkyl group, with an organometallic reagent of formula  $R_xMgX$  or  $R_xLi$  in which  $R_x$  is a  $C_{1-2}$  alkyl group and X is halo, in the presence of a solvent, at a temperature in the range of  $-50^{\circ}C$  to the boiling point of the solvent used to give compounds of Formula I in which  $R_4$  represents a group of formula  $-C(OH)R_xR_y$  in which  $R_x$  and  $R_y$  are the same  $C_{1-2}$  alkyl group; or

10 n) reacting compounds of Formula VI, in which  $R_y$  represents hydrogen or a  $C_{1-4}$  alkyl group, and A,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , n and g are as previously defined, with a phosphonium salt of formula  $R_zPh_3P^+Br^-$  in which  $R_z$  represents a  $C_{1-5}$  alkyl group or a benzyl group in the presence of a base, in a solvent at a temperature in the range  $-78^{\circ}C$  to the boiling point of the solvent used to give compounds of Formula I in which  $R_4$  represents a  $C_{2-6}$  alkenyl group in which the double bond is attached to the carbon alpha to the thiazole ring or a styryl group; or

15 o) reacting a compound of Formula I in which  $R_4$  represents halo and A,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , n and g are as previously defined or a compound of Formula V, with a compound of formula  $R_bMgX$  or  $R_bLi$  in which  $R_b$  is a  $C_{1-6}$  alkyl group and X is halo, in the presence of a solvent at a temperature in the range  $-78^{\circ}C$  to the boiling point of the solvent used, and then reacting the product obtained with an acylating agent of Formula  $R_cCON(CH_3)OCH_3$  in which  $R_c$  represents a  $C_{1-5}$  alkyl group in a solvent, at a temperature in the range  $0^{\circ}C$  to the boiling point of the solvent used to give compounds of Formula I in which  $R_4$  represents a  $C_{2-6}$  alkanoyl group; or

20 p) reacting a compound of Formula I in which  $R_4$  represents a hydroxy $C_{1-3}$  alkyl group, and A,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , n and g are as previously defined, with a  $C_{1-3}$  alkylating agent, in the presence of a base, in a solvent, at a temperature in the range of  $-50$  to  $150^{\circ}C$  to give compounds of Formula I in which  $R_4$  represents a  $C_{1-3}$  alkoxy $C_{1-3}$  alkyl group; or

25 q) reacting a compound of Formula I in which  $R_4$  represents a hydroxy $C_{1-3}$  alkyl group, and A,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , n and g are as previously defined, with a  $C_{4-7}$

cycloalkylalkylating agent, in the presence of a base, in a solvent, at a temperature in the range of -50 to 150°C. to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>4-7</sub>cycloalkylalkoxyC<sub>1-3</sub>alkyl group; or

5 r) reacting a compound of Formula I in which R<sub>4</sub> represents a hydroxyC<sub>1-3</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a C<sub>3-7</sub> alkynylalkylating agent in the presence of a base, in a solvent, at a temperature in the range of -50 to 150°C to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>3-7</sub> alkynylalkoxyC<sub>1-3</sub>alkyl group; or

10 s) reacting a compound of Formula I in which R<sub>4</sub> represents a mercaptoC<sub>1-3</sub> alkyl group, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a C<sub>1-3</sub> alkylating agent, in the presence of a base, in a solvent, at a temperature in the range of -50 to 150°C to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkylthioC<sub>1-3</sub> alkyl group; or

15 t) reacting a compound of Formula I in which R<sub>4</sub> represents halo or a compound of Formula V with a metallating agent of formula RMgX or RLi in which R is a C<sub>1-6</sub> alkyl group and X is halo, in a solvent, at a temperature in the range of -100°C to the boiling point of the solvent used to give an intermediate complex, which is reacted with a disulphide of formula R<sub>d</sub>S-SR<sub>d</sub> in which R<sub>d</sub> is a C<sub>1-3</sub> alkyl group or an aryl group, at a temperature in the range of -100°C to the boiling point of the solvent used to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkylthio group or an arylthio group and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined; or

20 u) reacting a compound of Formula I in which R<sub>4</sub> represents halo with an C<sub>1-3</sub> alkoxide salt, optionally in the presence of a solvent, optionally in the presence of a catalyst, at a temperature in the range of 0-350°C to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>1-3</sub> alkoxy group and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined; or

25 v) reacting a compound of Formula I in which R<sub>4</sub> represents halo, for example bromo or chloro, and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, or a compound of Formula V with a compound of formula R<sub>b</sub>MgX or R<sub>b</sub>Li in which R<sub>b</sub> is a

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C<sub>1-6</sub> alkyl group and X is halo, for example bromo or chloro, in the presence of a solvent, at a temperature in the range -78°C to the boiling point of the solvent used, and then reacting the product obtained with an alkenylating agent, for example a C<sub>3</sub>-alkenylmethyl halide, in a solvent, at a temperature in the range 0°C to the boiling point of the solvent used, to give compounds of Formula I in which R<sub>4</sub> represents a C<sub>3-6</sub> alkenyl group in which the double bond is not attached to the carbon alpha to the thiazole ring; or

w) reacting compounds of Formula VI, in which R<sub>y</sub> represents hydrogen and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a phosphonate of formula Me<sub>2</sub>NCH[PO(CR<sub>2</sub>)<sub>2</sub>]<sub>2</sub> in which R<sub>2</sub> represents a C<sub>1-4</sub> alkyl group in the presence of a base, in a solvent, at a temperature in the range -78°C to the boiling point of the solvent used, then subjecting the resulting intermediate product to partial hydrolysis in the presence of an acid, to give compounds of Formula I in which R<sub>4</sub> is a C<sub>3</sub>-alkoxycarbonylalkyl group; or

x) reacting compounds of Formula VI, in which R<sub>y</sub> represents hydrogen and A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, n and g are as previously defined, with a compound of Formula (R<sub>2</sub>O)<sub>2</sub>POCH<sub>2</sub>COR<sub>c</sub> in which R<sub>2</sub> represents a C<sub>1-2</sub> alkyl group and R<sub>c</sub> represents a C<sub>1-3</sub> alkyl group in the presence of a base, in a solvent, at a temperature in the range -78°C to the boiling point of the solvent used, then subjecting the resulting intermediate product to reaction with a reducing agent, in a solvent, at a temperature in the range -20°C to the boiling point of the solvent used, to give compounds of Formula I in which R<sub>4</sub> is a C<sub>4-6</sub>hydroxyalkenyl group in which the double bond is attached to the carbon alpha to the thiazole ring.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 00/04279

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07D513/04 A61K31/4188 A61K31/519 A61P25/00  
 //((C07D513/04, 277:00, 235:00), (C07D513/04, 277:00, 239:00))

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                              | Relevant to claim No. |
|------------|---|-----------------------|
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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